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Review Article

Eosinophilic Esophagitis: State of the Art in 2024

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Abstract

Eosinophilic esophagitis (EoE) is an immune-mediated and allergic disease categorized as a primary eosinophilic gastrointestinal disorder. Its incidence and prevalence have increased over the past decades, alongside growing awareness of the condition among gastroenterologists. EoE is more common in young males with a history of atopy. Diagnostic criteria include symptoms and esophageal histology showing a count of ≥15 eosinophils per high-power field or > 60 eosinophils/mm², with eosinophilia restricted to the esophagus and other causes of eosinophilia excluded. Treatment follows the "3 Ds" approach: diet, drugs, and endoscopic dilation. Recently approved biological therapies, such as dupilumab, and novel therapeutic strategies are under investigation for managing this condition.

Keywords

Eosinophilic esophagitis, esophagitis, eosinophilia, diagnosis, treatment.

INTRODUCTION

The term *eosinophil* was introduced by Paul Ehrlich to describe cells with granules that displayed an affinity for eosin and other acidic dyes[1]. Eosinophilic gastrointestinal (GI) disorders are characterized by eosinophilic infiltration of the GI tract accompanied by GI symptoms, in the absence of other known causes of eosinophilia[2]. Eosinophilic esophagitis (EoE) is classified as one of the primary eosinophilic disorders[2]. The first case of EoE was described in 1978 by Landres and colleagues, who interpreted it as a motility disorder resembling achalasia[3]. Subsequently, in 1982, eosinophilia in the esophagus was documented, although it was misinterpreted as a diagnostic biomarker for gastroesophageal reflux disease (GERD)[4]. It took two decades for EoE to be recognized as a distinct entity, following the publication of two case series. The first, by Attwood and colleagues in the United States in 1993, reported 12 patients with dysphagia, esophageal eosinophilia, and normal 24-hour pH monitoring; the second, by Straumann and colleagues in Switzerland in 1994, involved 10 patients with dysphagia. Both series identified EoE as more prevalent in males with atopic conditions and noted endoscopic findings distinct from those observed in GERD patients[5,6]. The first expert consensus on the diagnosis and management of EoE, published in 2007, significantly advanced the recognition and diagnosis of this condition, shaping current practices[7,8]. This review provides a com-

prehensive overview of the epidemiology, pathophysiology, diagnosis, and treatment of EoE.

EPIDEMIOLOGY

The incidence and prevalence of EoE are increasing globally in both pediatric and adult populations. A recent systematic review, encompassing 40 studies conducted between 1976 and 2022, included data from 288 million participants and 147,668 EoE cases across 15 countries spanning five continents. The global incidence of EoE was found to be 5.31 cases per 100,000 person-years (95% confidence interval [CI]: 3.98–6.63), while the global prevalence was 40.04 cases per 100,000 population (95% CI: 31.10–48.98). The condition is more common in males and in developed countries, with higher prevalence observed in North America compared to Europe, and its incidence and prevalence have increased over time—27.2- and 9.1-fold, respectively, compared to studies conducted before the year 2000[9]. This trend may be attributed to a global rise in immune-mediated diseases, increased awareness and interest in EoE, recent changes in diagnostic criteria, environmental factors such as modifications in food production (e.g., milk processing), antibiotic overuse, and improved diagnostic capabilities. Enhanced suspicion of EoE, greater access to upper endoscopy, and routine esophageal biopsy collection by gastroenterologists also contribute to these findings[10,11].

There is a male predominance in EoE, with a male-to-female ratio of 3:1[12]. More than 65% of cases occur during childhood and adolescence, with a peak prevalence between 30 and 44 years of age[13]. In Latin America, there is a scarcity of published epidemiological data. A Colombian study conducted in children and adolescents, which included 46 patients (31 males), found an average age of 11.8 years (range: 11 months–18 years), with 69% of the cases occurring in adolescents[14]. Another recent study involving a Colombian adult population, which included 152 patients (58.6% male), reported an average age of presentation of 43.3 years (range: 18–79 years), with 51.3% of cases occurring in the fourth and fifth decades of life[15].

A strong familial association has been observed, with a relative risk ranging from 10- to 64-fold, particularly in siblings, parents, and males. Concordance rates have been reported as 57.9% in monozygotic twins, 36.4% in dizygotic twins, and 2.4% in non-twin siblings. However, an analysis of twin cohorts revealed a significant role of shared environmental factors (81%) compared to genetic heritability (14.5%)[16]. A recent study identified 35 cases (14.6%) of EoE among 239 relatives of 37 EoE patients, with a higher prevalence in males than females ($p = 0.027$) and in individuals with atopic symptoms[17]. Numerous genome-wide association studies (GWAS) have been conducted to identify associated genetic *loci*, with particular focus on chemokine ligand 26 (CCL26) and calpain 14 (CAPN14)[18].

PATHOPHYSIOLOGY

EoE is a chronic inflammatory disease driven by a type 2 cellular response, in which type 2 helper T cells (T_h2) play a central role in the adaptive immune response. Type 2 cellular responses are involved in defense against parasites, venoms, and toxins, as well as in allergic diseases. It is thought that type 2 cellular responses are initiated in epithelial tissues through the production of alarmins (interleukin [IL]-25, IL-33, and thymic stromal lymphopoietin), which can activate both innate and adaptive immune responses. Alarmins released by the epithelium activate innate lymphoid cells, which subsequently release large amounts of IL-5, IL-9, and IL-13, thereby activating effector cells such as eosinophils, macrophages, basophils, and mast cells. Mast cells and basophils serve as additional sources of type 2 cytokines, particularly IL-4 and IL-13. IL-5 is critical for the development, growth, maturation, activation, and survival of eosinophils. IL-4 and IL-13 play key roles in T_h2-mediated inflammation, significantly affecting epithelial barrier permeability. IL-4 inhibits eosinophil apoptosis and induces their chemotaxis by upregulating eotaxin-3 expression, while both IL-4 and IL-13 contribute to tissue remodeling, including collagen deposition and angiogenesis[20,21]. EoE is characterized by the expression of a unique esophageal transcriptome[21].

There is also evidence supporting an allergic etiology in EoE. A high prevalence of atopic diseases, such as bronchial asthma, has been documented in these patients. Furthermore, eliminating certain foods from the diet induces clinical remission of the disease, with recurrence upon reintroduction of the same foods[21]. This condition is characterized by non-IgE-mediated food hypersensitivity, with increased expression of IgG4[22,23]. A summary of the pathophysiology is provided in **Figure 1**[24].

DIAGNOSIS

EoE is a chronic immune-allergic inflammatory disease. In a 2018 expert consensus, EoE was defined as a condition characterized by symptoms of dysphagia or food impaction in adults, and feeding difficulties, abdominal pain, or vomiting in children. Histologically, it is identified by eosinophil counts of ≥15 eosinophils per high-power field (HPF) or >60 eosinophils/mm² in esophageal tissue, with eosinophilia restricted to the esophagus[25]. The presence of atopic conditions and endoscopic findings—such as rings, longitudinal furrows, mucosal edema, white exudates, strictures, and mucosal tears—heightens diagnostic

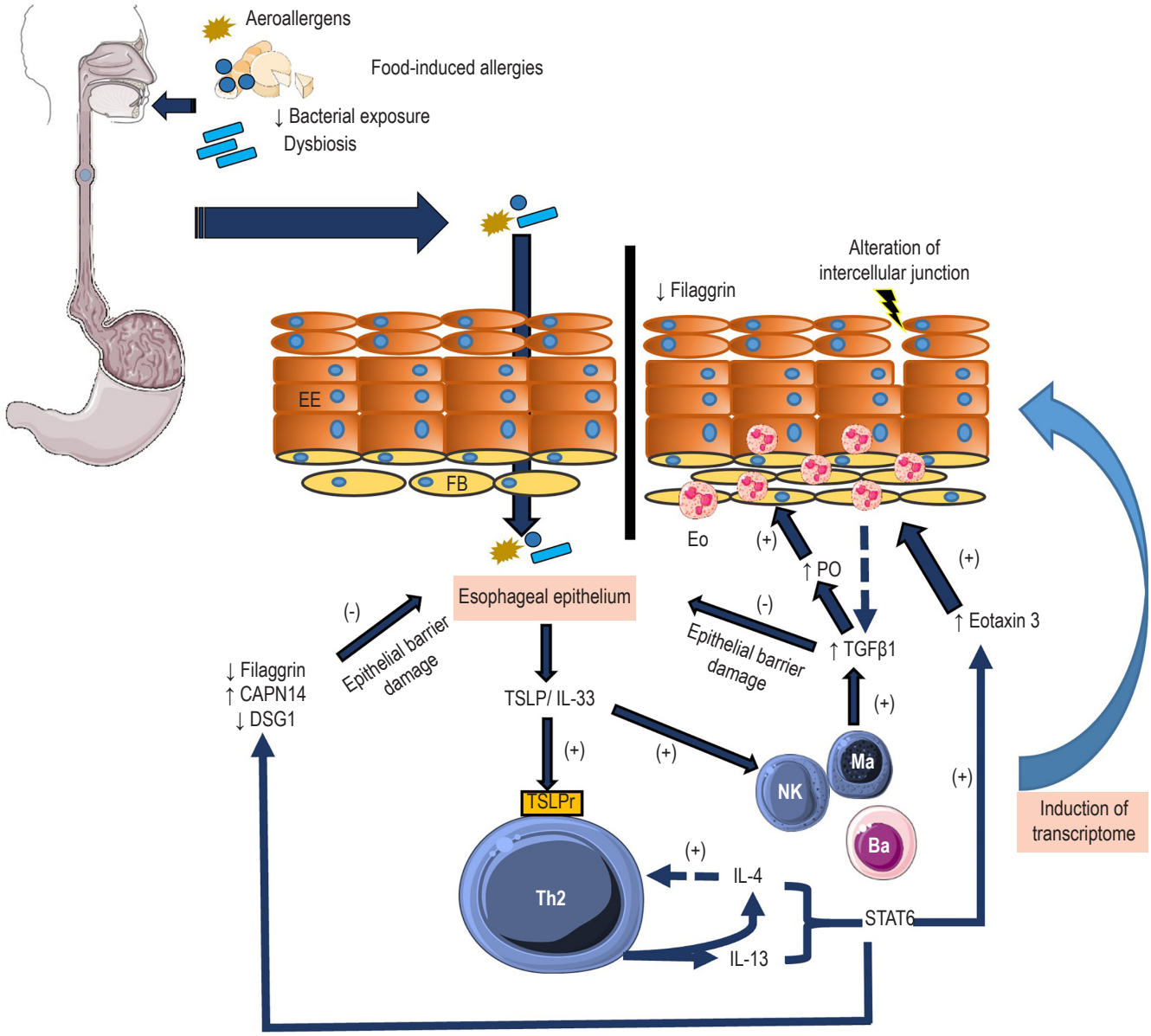


Figure 1. Pathophysiology of Eosinophilic Esophagitis. Ba: Basophils; CAPN14: Calpain 14; DSG1: Desmoglein-1; EE: Esophageal Epithelium; Eo: Eosinophils; FB: Fibroblasts; IL: Interleukin; Ma: Mast cells; NK: Natural Killer Cells; PO: Periostin; STAT6: Signal Transducer and Activator of Transcription 6; TGFβ1: Transforming Growth Factor Beta 1; Th2: Type 2 T Helper Cells; TSLP: Thymic Stromal Lymphopoietin; TSLPr: Thymic Stromal Lymphopoietin Receptor. Adapted from: Gómez-Aldana A, and colleagues. World J Gastroenterol. 2019;25(32):4598–4613[24].

suspicion. Additionally, other causes of eosinophilia, including achalasia, Crohn's disease, celiac disease, drug reactions, graft-versus-host disease, connective tissue diseases, eosinophilic gastroenteritis, vasculitis, and infections (e.g., fungal or viral), must be ruled out. EoE and GERD are not mutually exclusive conditions, and a therapeutic trial with proton pump inhibitors (PPIs) is not required to establish an EoE diagnosis[25]. A diagnostic algorithm is shown in **Figure 2**[11].

The three pillars of EoE diagnosis are symptoms, histology, and endoscopic findings. In young children, symptoms are non-specific, including nausea, vomiting, food refusal, abdominal pain, and growth retardation. In older children and adults, the disease manifests with heartburn, chest pain, dysphagia for solids, and food impaction. Several indices are available to quantify dysphagia in EoE, with the Dysphagia Symptom Questionnaire (DSQ) being the most frequently mentioned[11,26]. In patients presenting

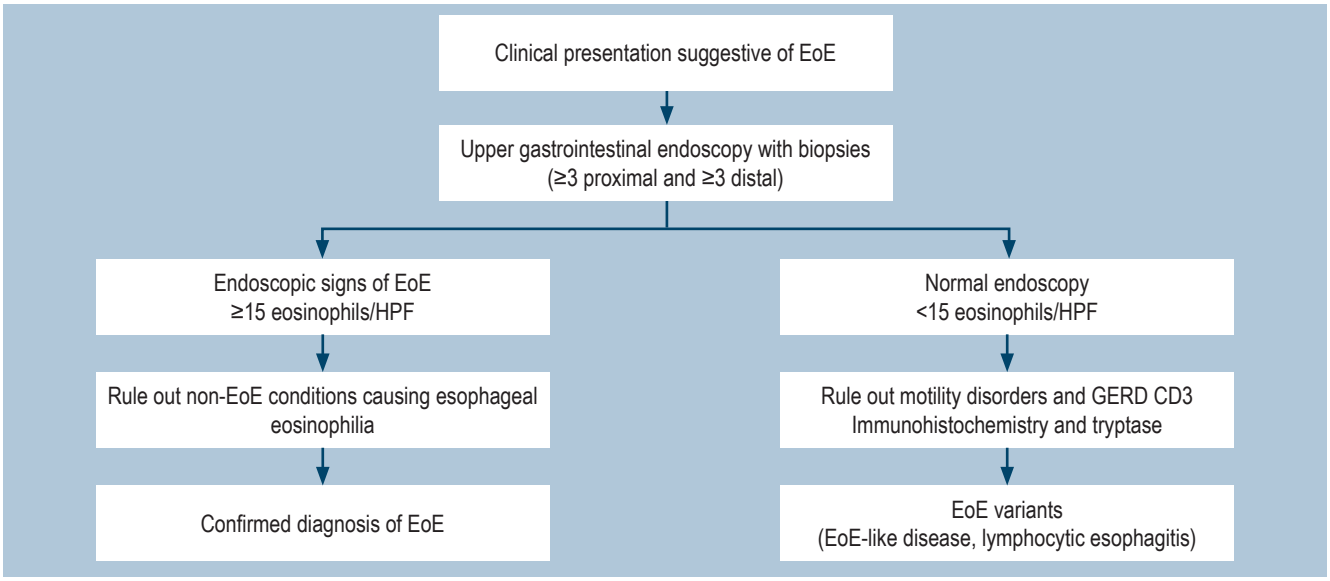


Figura 2. Diagnosis of Eosinophilic Esophagitis. HPF: High-Power Field; EoE: Eosinophilic Esophagitis; GERD: Gastroesophageal Reflux Disease. Adapted from: Biedermann L, and colleagues. Nat Rev Gastroenterol Hepatol. 2023;20(2):101–119[11].

with dysphagia for solids, the initial study is an upper digestive endoscopy. In EoE, only 5% of esophageal mucosa appears endoscopically normal.

An endoscopic scoring system has been developed to assess disease severity, known as the Endoscopic Reference Score (EREFS). This score evaluates five key endoscopic features (**Figure 3**): edema, rings, exudates, furrows, and strictures. The score ranges from 0 to 9, with higher scores indicating greater severity. The EREFS score is the standard tool that should be routinely used to ensure uniform terminology among gastroenterologists when describing endoscopic findings in EoE patients[27]. A recent endoscopy consensus on EoE recommends taking three biopsies from the proximal esophagus and three from the distal esophagus for diagnostic confirmation and patient follow-up[28]. Beyond the threshold of ≥15 eosinophils per high-power field (HPF), additional histological changes such as spongiosis, basal zone hyperplasia, mastocytosis, and papillary elongation are often observed in EoE patients[29]. A new severity index for EoE (I-SEE), proposed by a multidisciplinary consensus of international experts, integrates clinical, endoscopic, and histological aspects to determine disease severity during consultations. A score of 0–6 indicates mild disease, 7–14 indicates moderate disease, and ≥15 indicates severe disease[30].

TREATMENT

The goals of EoE treatment are to control symptoms and inflammation to prevent complications such as the development of strictures and food impaction. To achieve these objectives, the 3D rule (diet, drugs, and dilation) has been recommended. Among these, diet is the only intervention targeting the underlying cause, while endoscopic dilation is solely symptomatic, with no effect on inflammation or the disease course. Observation is not a treatment option for EoE; once diagnosed, patients must begin therapy to induce and maintain remission due to the high risk of recurrence[11].

Diet

The inflammatory response in EoE patients is triggered by exposure of the esophageal epithelium to food proteins. Consequently, elemental diets have demonstrated high rates of clinical, endoscopic, and histological remission. The first study on exclusive amino acid-based diets dates back to 1995, involving 10 children with EoE initially attributed to refractory GERD[31]. A systematic review of six observational studies reported histological remission with elemental diets in 93.6% of patients, compared to 13.3% with placebo (relative risk [RR]: 0.07; 95% confidence interval [CI]: 0.05–0.12)[32].

Despite this, maintaining dietary management in EoE patients remains challenging due to the lack of reliable tests to identify specific food triggers. International guidelines also do not recommend such tests, leaving the choice of foods to restrict largely empirical, based on their allergenic potential. Strict adherence to dietary restrictions is difficult as it significantly impacts patients' quality of life. The goal of dietary management in EoE is to minimize exposure to inflammatory

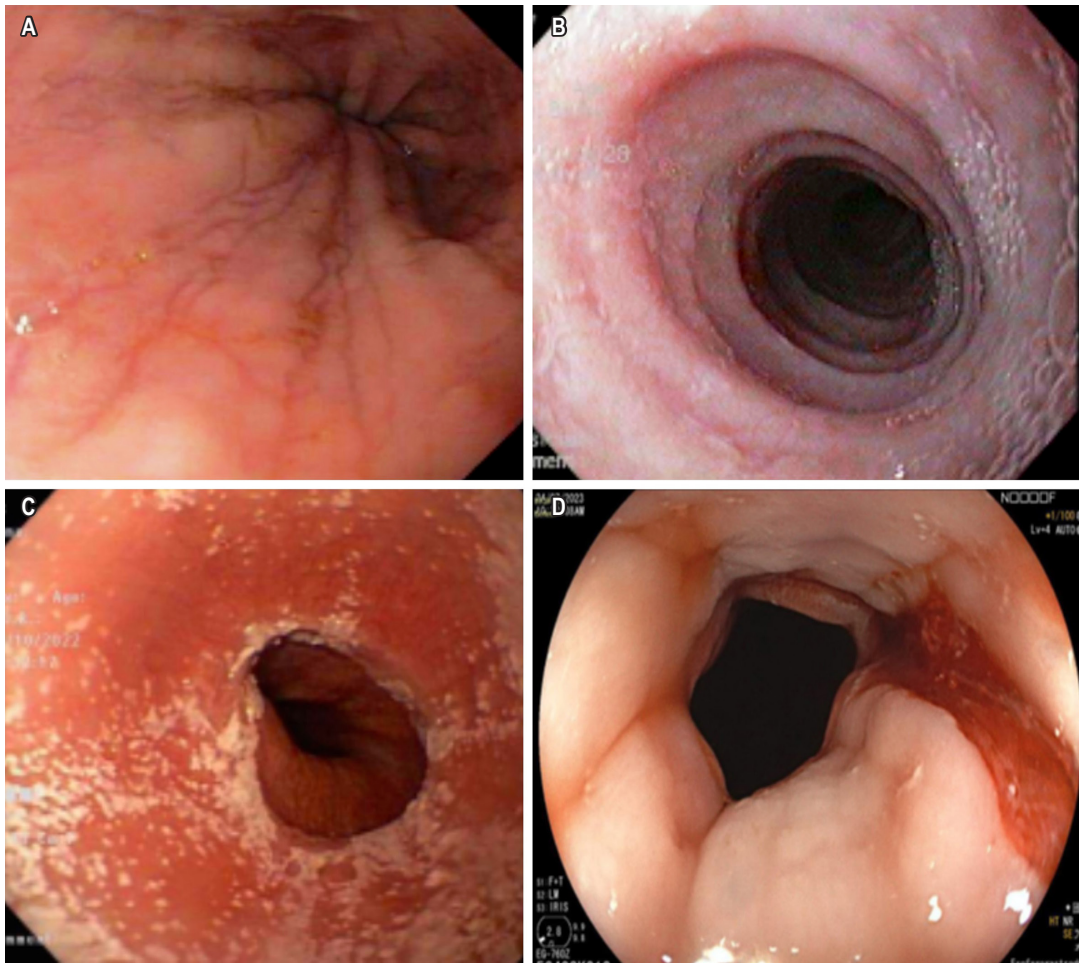


Figure 3. Endoscopic Findings in Eosinophilic Esophagitis. **A.** Edema and longitudinal furrows. **B.** Rings. **C.** White exudates. **D.** Mucosal tear. Author's file.

triggers while ensuring adequate nutrition and preserving patients' quality of life to the greatest extent possible[11].

The six-food elimination diet (SFED), targeting common allergenic foods (cow's milk, wheat, soy, eggs, nuts, and seafood), was the first regimen applied to both children and adults with EoE. It demonstrated better adherence than elemental diets, though reintroducing foods is time- and cost-intensive, requiring endoscopy with esophageal biopsies to identify specific triggers of eosinophilia. Nevertheless, these studies have highlighted the relative allergenicity of specific foods; for instance, cow's milk and wheat are more allergenic than nuts and seafood, leading to the exploration of less restrictive dietary approaches[33]. A systematic review of elimination diets in EoE, encompassing 34 studies and 1,762 patients, evaluated SFED, a four-food elimination diet (FFED: dairy, wheat, eggs, and soy), dairy-only elimination, and allergy-directed elimination diets. Histological remission rates were reported as 61.3% (95% CI: 53.0%–69.3%), 49.4% (95% CI: 32.5%–66.3%), 51.4% (95% CI: 42.6%–60.1%), and 45.7% (95% CI: 32.0%–59.7%), respectively, while clinical response rates were 92.8% (95% CI: 81.2%–99.6%), 74.1% (95% CI: 49.8%–92.6%), 87.1% (95% CI: 58.4%–99.9%), and 69.0% (95% CI: 50.2%–85.3%)[33]. A more recent randomized, multicenter study involving 129 adults with EoE found no significant differences in histological remission between SFED and dairy-only elimination after six weeks of follow-up (40% versus 34%; $p = 0.58$; 95% CI: 11–23)[34]. Based on these findings, it is advisable to initiate dietary treatment with dairy elimination in motivated EoE patients. Depending on the response, additional food groups can be excluded as needed.

Drugs

Steroids

The first reported experience with steroids in EoE was published in 1998, involving 20 pediatric patients with GERD symptoms refractory to antireflux treatment, who showed good response to oral methylprednisolone[35]. Subsequently, steroids administered via inhalation chambers with subsequent swallowing were used. A systematic review of eight randomized controlled trials comparing topical steroids with placebo found that 64.9% of patients achieved histological remission compared to 13.3% of those treated with placebo (RR: 0.39; 95% CI: 0.26–0.58). Adverse events occurred in 43% of the steroid group compared to 36% in the placebo group (RR: 1.0; 95% CI: 0.85–1.19)[32]. The recommended dose of fluticasone propionate is 880–1760 µg/day, administered as 2–4 puffs twice daily, with each puff containing 125–250 µg depending on the formulation. The recommended dose of budesonide is 2–4 mg/day, administered twice daily[36].

New formulations of topical swallowed steroids are now available, including effervescent orally dispersible budesonide, approved by the European Medicines Agency (EMA) in 2018, and oral viscous budesonide suspension, approved in February 2024 in the United States. Ongoing studies are investigating orodispersible fluticasone tablets[11]. Patients are advised not to eat or drink for 30–60 minutes after administration and to rinse their mouths afterward to prevent oral candidiasis. Reported adverse effects include oral candidiasis (1%), esophageal candidiasis (5%–30%), and adrenal insufficiency in 16% of patients[24].

Proton Pump Inhibitors (PPIs)

Several mechanisms explain the response of EoE patients to PPI therapy. First, PPIs have antisecretory effects, increasing the pH of refluxate, which restores esophageal mucosal integrity and prevents the dilation of intercellular spaces, reducing inflammation and restoring the epithelial barrier. Additionally, PPIs exhibit anti-inflammatory properties: they block adhesion molecules, preventing the activation of pro-inflammatory cytokines; inhibit STAT6 activation, which mediates eotaxin-3 expression for eosinophil recruitment; and block IL-13, thereby preventing eosinophil activation[37]. A systematic review of 23 observational studies found that patients treated with PPIs achieved histological remission in 41.7% of cases, compared to 13.7% with placebo (RR: 0.66; 95% CI: 0.61–0.72)[32]. Moderate (20 mg) or high (40 mg) doses of PPIs administered twice daily are recommended[38]. Most patients maintain clinical and histological remission with PPI doses of 40 mg/day or less[39].

Potassium-Competitive Acid Blockers (P-CABs)

This novel group of acid-blocking drugs may serve as an alternative for treatment. In cells from EoE patients, P-CABs have demonstrated anti-inflammatory effects similar to PPIs, seemingly mediated by a non-gastric proton pump that regulates T_h2 cytokine-stimulated eotaxin-3 secretion[40]. The first case series, published in Japan in 2016, involved four patients who failed to achieve histological remission with esomeprazole 20 mg/day over three months[41]. In a retrospective study, vonoprazan showed efficacy comparable to PPIs in terms of symptomatic, endoscopic, and histological responses in EoE patients[42].

Biologic Therapy

For patients with severe or refractory EoE unresponsive to conventional treatment, biologic therapy has been proposed. Based on the disease's pathophysiology, clinical trials have investigated agents targeting IL-4/IL-13 and IL-5 pathways. Among these, the most extensively studied is dupilumab, a humanized IgG4 monoclonal antibody that blocks the α-chain of the IL-4 receptor (IL-4Rα), shared by IL-4 and IL-13, thereby inhibiting their signaling[43]. A phase III randomized, controlled, multicenter trial involving 81 patients with EoE demonstrated histological remission in 60% of patients treated with subcutaneous dupilumab 300 mg weekly compared to 5% in the placebo group ($p < 0.001$) after 24 weeks of follow-up. The response was sustained at 52 weeks, with an acceptable safety profile[44]. A recent study in patients aged 1 to 11 years with EoE refractory to PPIs also confirmed the efficacy and safety of dupilumab compared to placebo[45]. In May 2022, the U.S. Food and Drug Administration (FDA) approved dupilumab for EoE as a first- or second-line therapy. However, in our setting, we recommend its use as a second-line treatment for patients with severe EoE refractory to conventional therapy.

Other biologics, such as anti-IL-5 monoclonal antibodies mepolizumab, reslizumab, and benralizumab, have been studied in EoE. While these agents reduce peripheral and tissue eosinophilia, their clinical efficacy—particularly for improving dysphagia—has been minimal[46–48].

Dilation

EoE is a chronic and progressive disease that, if not treated promptly and adequately, leads to esophageal wall remodeling and rigidity, resulting in stricture formation[49]. A study of 200 EoE patients demonstrated that the prevalence of esophageal strictures increases with diagnostic delay, rising from 17.2% with a delay of two years to 70.8% when the delay exceeds 20 years ($p < 0.001$)[50]. Mechanical dilation has proven effective for alleviating symptoms such

as dysphagia and is considered safe for patients, though it does not address inflammation. The two most commonly used dilation techniques are pneumatic balloon dilation and Savary-Gilliard dilators. Recently, a transparent conical device called BougieCap, available in various diameters, has been used. It attaches to the endoscope tip and enables direct visualization during dilation, showing clinical improvement and safety in a study involving 50 EoE patients[51]. A systematic review of 27 studies, encompassing 845 patients with strictures (including 87 children), evaluated the outcomes of 1,820 esophageal dilations, with an average of three dilations per patient. Clinical response was achieved in 95% of cases, with a perforation rate of 0.38%, bleeding rate of 0.05%, and hospitalization rate of 0.67%. No deaths related to dilation were reported[52]. Dilation is recommended for cases of stricture, but if active EoE is present, additional treatment modalities—such as dietary therapy, PPIs, steroids, or a combination of these—are required. Ideally, inflammation should be controlled first, with dilation reserved for patients experiencing persistent dysphagia or strictures.

PROPOSED MANAGEMENT OF EoE

Diet, PPIs, and steroids are considered first-line treatments for controlling inflammation in EoE patients. Biologic therapy with dupilumab is a second-line treatment for patients with severe, refractory EoE or concurrent atopic conditions, such as eczema, moderate-to-severe asthma, and chronic rhinosinusitis with nasal polyposis[53]. Endoscopic dilation is reserved for patients with persistent strictures despite achieving inflammation control with medical therapy.

When comparing the various therapeutic options, proton pump inhibitors (PPIs) are low-cost, easy to use, and well-tolerated. However, their response rates as monotherapy range between 30% and 50%, and they are less effective for the fibrostenotic phenotype. Elimination diets are natural and free of adverse events, with rare cases of nutritional deficiencies, but long-term adherence is challenging, and repeated endoscopies with biopsies are necessary to monitor response. Swallowed steroids are more effective than PPIs but are more expensive and associated with adverse events such as esophageal candidiasis. Dupilumab is effective but requires weekly subcutaneous injections, with potential adverse effects including injection site infections and conjunctivitis. There is no consensus on the preferred initial treatment for EoE. Therefore, medical management depends on the physician's experience, the patient's motivation (adherence), and the availability or approval of medications in each country, particularly topical steroid formulations and dupilumab. Data on combination therapies in EoE remain limited[53,54].

Similar to the approach used in inflammatory bowel disease (IBD), both a step-up treatment strategy and an aggressive early treatment strategy (top-down) have been proposed, as illustrated in **Figure 4**[54]. The top-down

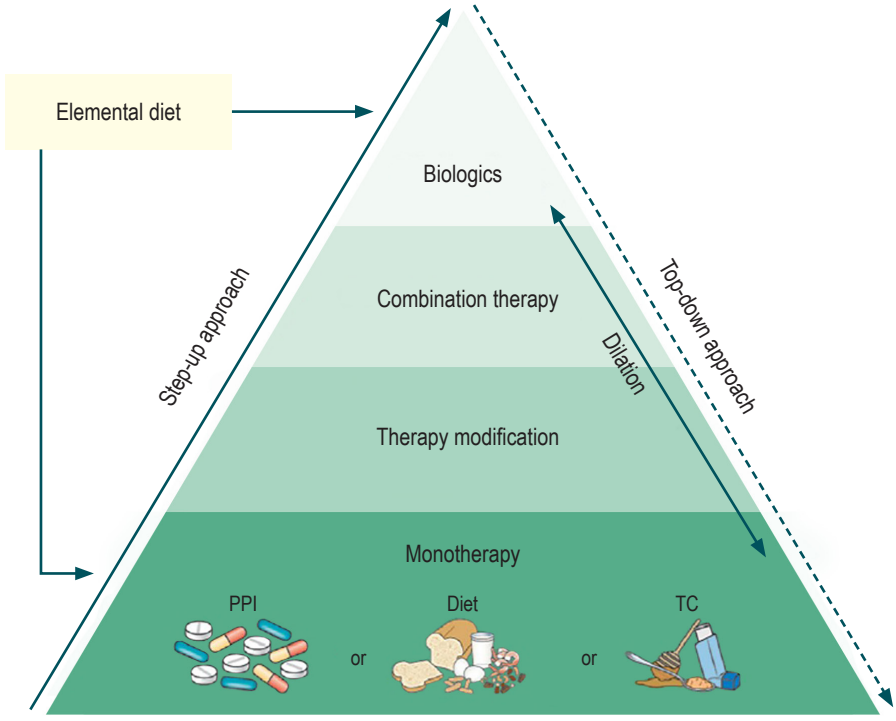


Figure 4. Therapeutic Pyramid in Eosinophilic Esophagitis. TC: Topical Corticosteroid; PPI: Proton Pump Inhibitor. Adapted from: Oliva S, and colleagues. Clin Gastroenterol Hepatol. 2024;22(9):1763–1769[54].

approach would be reserved for severe cases, fibrostenotic phenotypes, or EoE coexisting with other atopic diseases. However, further studies are needed to evaluate the utility and cost-effectiveness of this strategy[55]. A survey conducted among 228 gastroenterologists from 18 European countries reported that 82.9% use PPIs as first-line therapy, 41.6% use topical steroids, 20.6% use elimination diets, and 9.2% use combination therapies. Additionally, 21.5% do not prescribe maintenance therapy[56].

Two critical aspects in the management of EoE are the need for maintenance therapy and disease monitoring. A multidisciplinary expert consensus on EoE concludes that maintenance therapy likely reduces the risk of complications and that regular, scheduled follow-up is necessary, rather than on-demand monitoring. This is due to the moderate correlation between symptoms and histological or endoscopic disease activity. It is essential to assess disease activity, monitor adverse drug events, adjust therapy, and ensure treatment adherence in all patients. To monitor disease activity, it is necessary to evaluate symptoms, determine eosinophil counts, and assess endoscopic activity using the EREFS scoring system. Endoscopy with esophageal biopsies should be performed 8–12 weeks after initiating induction therapy. If there is a positive response, maintenance therapy should be continued. The need for re-evaluation with endoscopy should be individualized, typically within one year. However, if there is no response and treatment adjustments are made, follow-up endoscopy with biopsies should be performed within 8–12 weeks[57]. A proposed treatment algorithm is shown in **Figure 5**[53].

CONCLUSION

EoE is a type 2 immune-mediated allergic disease that is complex, multifactorial, chronic, and progressive. It is a relatively recent discovery, with defined diagnostic criteria, and its prevalence and incidence are increasing worldwide. Timely diagnosis and appropriate treatment are essential to prevent long-term complications. Key therapeutic approaches include dietary management, topical steroids, and PPIs, with endoscopic dilation required in cases of strictures. New biologic therapies, such as dupilumab, have demonstrated efficacy and safety in EoE, and innovative therapeutic strategies for the management of this condition are under investigation.

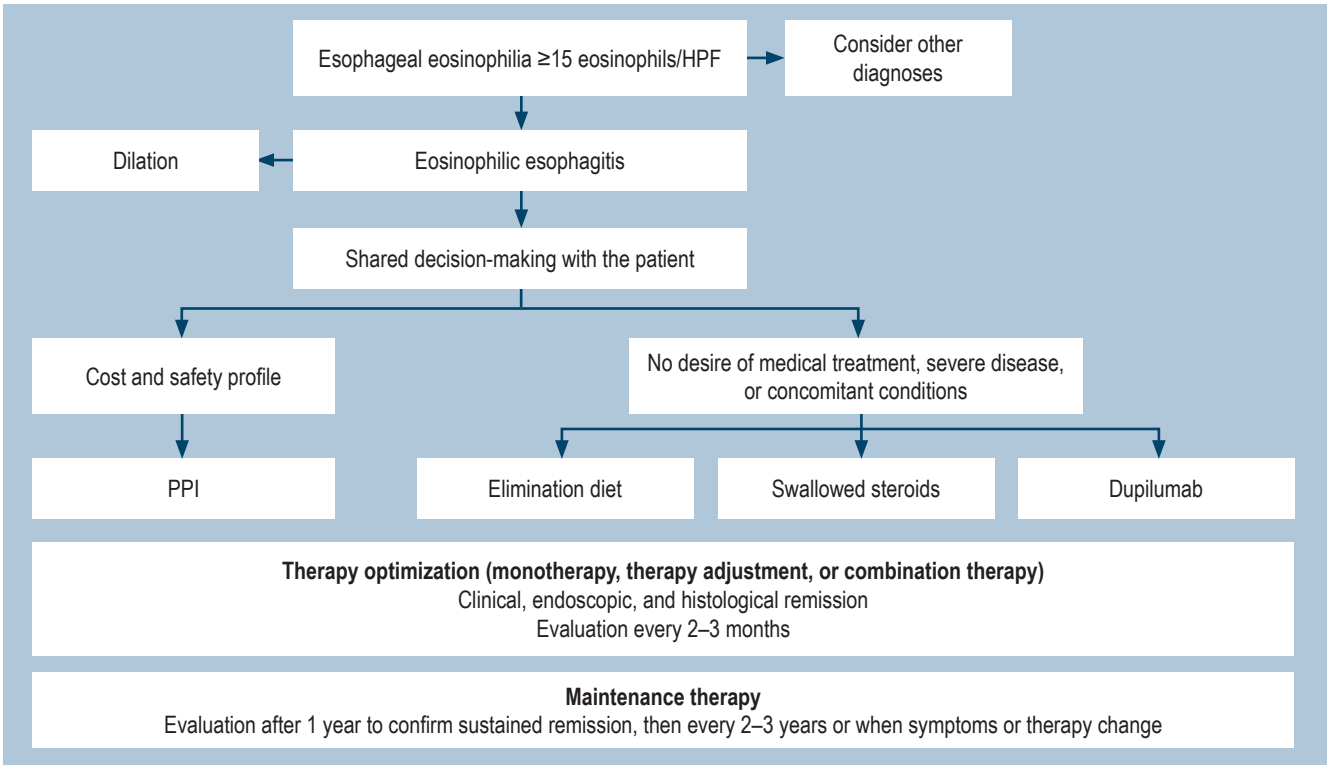


Figure 5. Management of Eosinophilic Esophagitis. HPF: High-Power Field; PPI: Proton Pump Inhibitor. Adapted from: Sauer BG, and colleagues. Am J Gastroenterol. 2023;118(5):780–783[53].

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