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# Eosinophilic Esophagitis: Pharmacotherapy Challenges and Advances

## Eozinofilni ezofagitis: suvremena farmakoterapija i izazovi

Mirjana Kalauz[1, 2*], Zmarak Kahn[1], Matija Kalauz[3], Zlatko Marušić[1, 4]

[1] University of Zagreb, School of Medicine, Zagreb, Croatia

[2] Clinical Hospital Center Zagreb, Department of Internal Medicine, Division of Gastroenterology and Hepatology, Zagreb, Croatia

[3] Emergency Medical Services of Karlovac County, Karlovac, Croatia

[4] Clinical Hospital Center Zagreb, Department of Pathology, Zagreb, Croatia

**Abstract.** Eosinophilic oesophagitis (EoE) is a chronic, immune-mediated disorder characterized by oesophageal dysfunction, Th2-driven inflammation, and tissue remodelling. Current pharmacological treatments, including proton pump inhibitors, topical corticosteroids and biologics offer varying efficacy and are often limited by relapse, adherence issues and incomplete symptom resolution. Dupilumab, targeting IL-4/IL-13 pathways, shows the most promising results to date, particularly in refractory cases. Novel biologics are under investigati aiming to address unmet needs in personalised EoE therapy. Despite advances, treatment selection remains complex and should be individualised. Future research should focus on biomarkers, long-term safety and optimising treatment access.

**Keywords:** biological products; eosinophilic esophagitis; glucocorticoids; proton pump inhibitors

**Sažetak.** Eozinofilni ezofagitis (EoE) jest kronični, imunološki posredovan poremećaj, karakteriziran upalom Th2, remodeliranjem tkiva i disfunkcijom jednjaka. Farmakoterapija se zasniva na primjeni inhibitora protonske pumpe, topičkih kortikosteroida i bioloških lijekova. Različita i djelomična učinkovitost ovih lijekova te česti relapsi bolesti ograničavaju uspjeh liječenja u svih bolesnika. Dupilumab, humano monoklonsko protutuijelo, inhibira dvostruke signalne puteve i IL-4 i IL-13 te se pokazao vrlo učinkovit, osobito u refraktornim slučajevima. Unatoč napretku u farmakoterapijskom pristupu ovim bolesnicima, odabir optimalnog lijeka i dalje predstavlja izazov. Buduća bi se istraživanja trebala usmjeriti evalvaciji biomarkera koji bi omogućili personaliziran pristup liječenju i procjeni dugoročno sigurne primjene lijekova.

**Ključne riječi:** biološki lijekovi; eozinofilni ezofagitis; inhibitori protonske pumpe; glukokortikoidi

*Corresponding author:
Assoc. Prof. Mirjana Kalauz, MD, PhD
Clinical Hospital Center Zagreb,
Department of Internal Medicine, Division of Gastroenetrology and Hepatology,
Kišpatićeva 12, Zagreb, Croatia
Mob: +38598519088
*E-mail:* mirjanakalauz1@gmail.com;
mirjana.kalauz@kbc-zagreb.hr

http://hrcak.srce.hr/medicina

## INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated disorder characterized by diverse clinical symptoms, as well as distinct endoscopic (Figure 1) and histopathologic features (Figure 2). Treatment responses can vary significantly among patients[1]. The estimated prevalence of EoE ranges from 0.5 to 1 case per 1,000 individuals, with higher rates reported in Western countries and a male-to-female ratio of approximately 3:1. Over time, the incidence has increased to 5–10 cases per 100,000 persons annually. Additionally, 50–70% of EoE patients have coexisting atopic conditions such as asthma, allergic rhinitis, or food allergies[2]. Although eosinophilic infiltration (>15 eosinophils per high-power field) is a main histologic feature of EoE, eosinophils represent the final step of an inflammatory cascade rather than the primary trigger. The disease is driven by type 2 helper T (Th2) cell responses, where allergens interact with a compromised oesophageal barrier, leading to the release of alarmins such as thymic stromal lymphopoietin (TSLP) and interleukin (IL)-33. These alarmins recruit Th2 lymphocytes, which then produce type 2 cytokines, including IL-4, IL-5, and

Eosinophilic esophagitis is a chronic type 2 immune-mediated disease with heterogeneous response to therapy. Proton pump inhibitors, topical corticosteroids and dietary elimination induce remission in only a subset of patients and do not target the underlying immune dysregulation, emphasizing the need for more effective and durable mechanism-based treatment strategies in clinical practice.

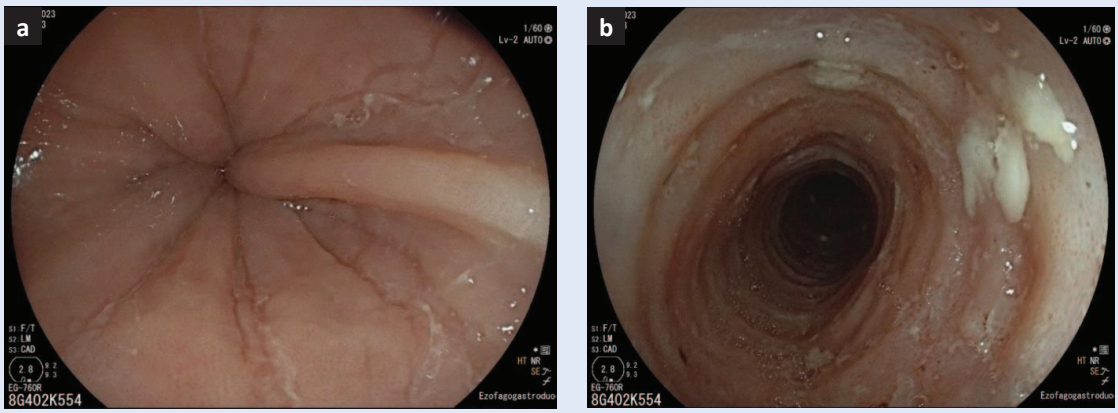


**Figure 1.** (a) linear furrowing and band of fibrosis can be seen endoscopically at the gastroesophageal junction (b) Concentric rings and white plaques can be seen lining the mucosa of the esophagus

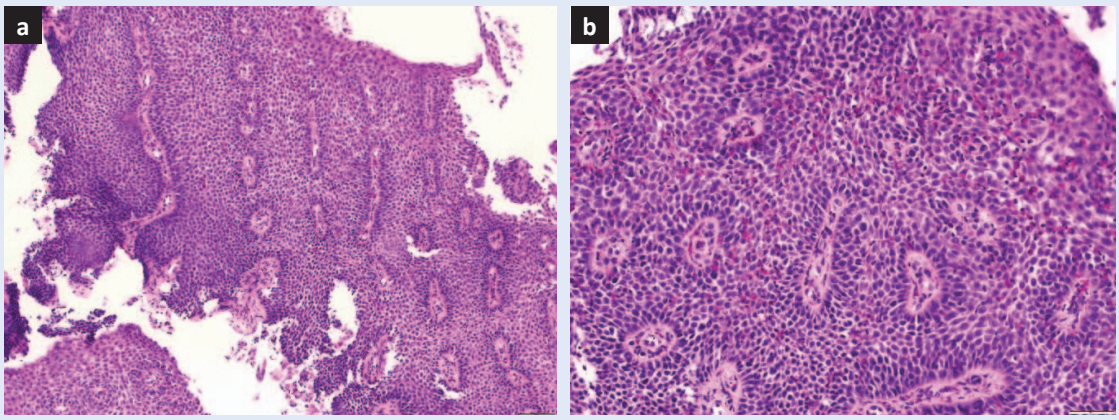


**Figure 2.** (a) histology show esophageal mucosa lined by multilayered squamous epithelium showing signs of inflammation (high papillae, intercellular oedema, basal layer hyperplasia) and (b) marked epithelial infiltration by eosinophils.

IL-13, ultimately driving eosinophil recruitment to the esophagus[3].

esophageal biopsies in EoE frequently reveal increased lymphocyte infiltration, with single-cell RNA analysis identifying various T-cell subtypes[4]. Mast cells, which contribute to fibrosis and smooth muscle dysfunction, often outnumber eosinophils and serve as a distinguishing feature from conditions like GERD[5]. Furthermore, other immune and structural cells, such as basophils, fibroblasts, NK cells, and esophageal epithelial cells, play significant roles in EoE pathogenesis, underscoring the disease's complexity beyond eosinophilic infiltration[6]. Transcriptomic studies of the esophagus have helped identify disease-specific molecular signatures and potential biomarkers for targeted therapies[7]. Genome-wide association studies (GWAS) have revealed genetic risk factors associated with EoE susceptibility and pathogenesis, highlighting key genes such as TSLP, IL-13, Calpain-14, and filaggrin mutations[8]. Diet remains the only non-pharmacological approach that targets the underlying cause of EoE. The limited practicality of elemental diets and the low diagnostic yield of allergy testing-directed food avoidance have led to the adoption of empirical elimination diets in the management of EoE. Stepwise elimination protocol such as two- or four-food elimination diet should be considered as first-line approach across all age groups[9].

Despite advances in understanding its pathophysiology, the pharmacologic management of EoE remains challenging. Current therapeutic options, including proton pump inhibitors (PPIs), topical corticosteroids, and biologics are limited by varying efficacy, adherence challenges, safety concerns, and inconsistent long-term control[10]. This unmet need in treatment underscores a critical gap in patient care and remains an active area of research[11].

## CURRENT PHARMACOLOGIC STRATEGIES AND THEIR LIMITATIONS

### 1. Proton Pump Inhibitors (PPIs): Inconsistent Response

Proton pump inhibitors (PPIs) are widely used as an initial therapeutic option for eosinophilic esophagitis (EoE) due to their favorable safety profile, cost-effectiveness, and accessibility[1]. PPIs effectively reduce symptoms and inflammation, particularly in patients with PPI-responsive esophageal eosinophilia (PPI-REE) or when reflux-like symptoms overlap with EoE[11]. A recent systematic review and meta-analysis evaluated the efficacy of PPIs in inducing and maintaining remission in EoE showing that PPIs are effective in achieving remission in nearly half of patients. The study also found that higher doses improved outcomes, and that remission could be sustained with reduced maintenance dosing[12]. One mechanism by which PPIs demonstrate benefit in EoE is by reducing esophageal acid exposure, which contributes to improved epithelial barrier function[13]. Acid reflux can damage the esophageal epithelium, increasing intracellular spaces and impairing the barrier. By decreasing acid exposure, PPIs help restore epithelial integrity and reduce inflammation[13].

Beyond acid suppression, PPIs have a direct anti-inflammatory effect by inhibiting eotaxin-3 expression in esophageal squamous cells, a key chemokine involved in eosinophil recruitment[14]. This occurs through the suppression of signal transducer and activator of transcription 6 (STAT6) binding to the eotaxin-3 promoter, thereby reducing eotaxin-3 production and eosinophil-driven inflammation[14]. In the past, a trial of PPIs was required to differentiate between PPI-REE and EoE. However, a 2018 expert consensus no longer separates the two, since they share similar features[15]. Now, PPIs are seen as a proper treatment for EoE, not just a way to diagnose it. Although PPIs have become an important first-line treatment for EoE, particularly in patients with PPI-REE, their efficacy is variable. Approximately 30-50% of patients achieve histologic remission with PPI therapy. However, PPIs do not directly modulate the underlying immune dysregulation in EoE, making them a less effective long-term monotherapy[16]. Additional research is needed to address unresolved questions about PPI therapy in PPI-REE, including long-term efficacy, optimal dosing, potential reversal of esophageal fibrosis, cost-effectiveness, and quality of life. Current efforts focus on identifying predictive biomarkers such as transcriptomic, genomic, proteomic, and

metabolomic profiles to guide personalized therapy by distinguishing between low-dose responders, high-dose responders, and non-responders, while also considering pharmacogenetic factors like CYP2C19*17 and STAT6 variants[17].

### 2. Topical Corticosteroids: Effective but Challenging

Swallowed corticosteroids play a crucial role in the management of eosinophilic oesophagitis (EoE). An analysis of data from a large European cohort of EoE patients (CONNECT database) identified topical corticosteroids as the most effective therapy for inducing both clinical and histological remission[18]. A technical review of eight double-blind, placebo-controlled clinical trials, including 437 patients treated for a mean duration of eight weeks, found that 64.9% of those receiving topical corticosteroids achieved histological remission, compared to only 13.3% in the placebo group[19]. Several factors have been associated with steroid non-response, including baseline oesophageal dilation, oedema or decreased vascularity observed on baseline endoscopy, the presence of a hiatal hernia, and increased body mass index[20]. The importance of maintenance therapy in patients who have achieved histological remission is emphasised by numerous studies, as relapse rates are high following corticosteroid discontinuation[21]. Moreover, untreated cases carry a potential risk of progression to fibrostenotic disease[22, 23]. A recent trial investigating maintenance budesonide over 48 weeks reported a rapid relapse upon discontinuation, with a median relapse time of 87 days, affecting 95.6% of patients who transitioned to placebo[24]. However, concerns persist regarding the long-term safety of sustained corticosteroid use[25]. The most frequently reported adverse effect of budesonide was asymptomatic oesophageal candidiasis, occurring in up to 16.2% of patients[26]. Various formulations of topical corticosteroids are currently under investigation in clinical trials. In the United States, off-label use is common, with corticosteroid inhalers originally designed for asthma being repurposed, or corticosteroids administered as compounded slurries[27]. In contrast, the European Medicines Agency (EMA) has approved budesonide in the form of orodispersible tablets for adults, which is widely used and considered safe[28]. Despite their efficacy, topical corticosteroids pose several challenges, including high relapse rates upon discontinuation, the risk of oesophageal candidiasis, the lack of standardised formulations affecting adherence, and suboptimal delivery mechanisms, which hinder long-term use and consistency[19].

### 3. Biologic Therapies: Progress and Barriers

In the last ten years, molecular therapies for EoE have evolved from pathophysiological concepts based on *in-vitro* studies to promising therapeutic options, now in phase 3 trials (Table 1).

#### *Anti IL-5 therapy: mepolizumab, reslizumab and benralizumab*

Eosinophils are a natural therapeutic target in EoE, and early trials targeting IL-5 with mepolizumab and reslizumab showed moderate decreases in eosinophil counts, but no symptom improvement[29, 30]. Recent studies addressed design flaws, but still found that despite significant histologic and endoscopic improvements with mepolizumab and benralizumab, symptoms like dysphagia did not improve significantly [31, 32]. These confounding results suggest that eosinophils may not be the sole driver of EoE, and other factors are likely contributing to persistent disease activity.

#### *Anti IL-4/IL13 therapy: dupilumab*

Recent evidence highlights the critical role of interleukin IL-4 and IL-13 in EoE[33, 34]. Dupilumab, a monoclonal antibody targeting IL-4R, inhibits the shared receptor for both IL-4 and IL-13[35], effectively reducing the chronicity and severity of EoE[36].

A meta-analysis on biologics indicates that therapies targeting IL-4/IL-13 significantly improve histological, clinical, and endoscopic outcomes in EoE, with dupilumab demonstrating superior long-term efficacy[37]. It has been approved for multiple eosinophilic inflammatory diseases, including EoE[38]. A recent phase 3 trial showed that weekly subcutaneous dupilumab led to substantial histological and clinical improvements in EoE patients unresponsive to at least eight weeks of proton pump inhibitor (PPI) therapy[39]. Furthermore, a real-world study on severe, refractory, and fibrosten-

otic EoE found significant increases in oesophageal diameter (from 13.9 to 16.0 mm) and symptom relief in 91% of patients ($p < 0.001$)[40]. Currently, it is the only biologic authorised by both the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for treating EoE in patients over 12 years old who weigh more than 40 kg[41, 42]. All major studies on dupilumab have focused on EoE cases refractory to conventional treatments[43]. In Europe, its use is restricted to patients who have either failed or cannot tolerate standard therapies[44]. However, the FDA does not mandate prior treatment failure for its prescription, making it a potential first-line option in select cases, such as patients with low adherence to dietary elimination or those with multiple atopic comorbidities (asthma, atopic dermatitis or chronic rhinosinusitis with nasal polyps), for which dupilumab is also approved[45]. Ongoing research is evaluating its efficacy in paediatric patients (1–11 years; 5–60 kg) (NCT04394351), long-term effects on oesophageal function (NCT06101095), and the impact of reintroducing EoE-triggering foods (NCT05247866)[46–48].

***Anti IL-13 therapy: cendakimab and dectrekumab***

Dectrekumab (QaX576) and cendakimab (RPC4046/CC-93538) are monoclonal antibodies that target IL-13. QaX576 blocks IL-13 activity and prevents eotaxin synthesis, while RPC4046/CC-93538 inhibits IL-13 from binding to its receptors, IL-13-Rα1 and IL-13-Rα2 [49, 50]. Additionally, cendakimab (RPC4046/CC-93538) is an IgG1k monoclonal antibody that targets IL-13, blocking its binding to both IL-13 receptors. In the HEROES trial, adult patients with active EoE treated with cendakimab (180 mg or 360 mg weekly) showed significant improvements in histopathological and endoscopic outcomes at week 16 compared to placebo[51]. However, clinical improvements in dysphagia were minimal, though the high-dose group exhibited a positive effect on disease severity. Active clinical trials are investigating the efficacy of cendakimab in both adults and adolescents (NCT04753697), as well as potential drug interactions (NCT05175352)[52, 53].

Dectrekumab (QAX576) is another anti-IL-13 monoclonal antibody, previously studied in other Th2 diseases. Although eosinophil counts significantly decreased in the treatment group (-60%), the primary endpoint (75% reduction in peak eosinophil counts) was not met. The treatment group demonstrated improved markers of inflammation, such as eotaxin-3 and periostin, indicating its potential in EoE management. Additionally, while there was a trend towards improved dysphagia, it was not statistically significant[54].

Biologic therapy, particularly dupilumab, achieves significant histologic, endoscopic and clinical improvement in refractory disease and represents a major step toward targeted treatment. High cost, limited accessibility and uncertain long-term safety remain important barriers. Future research should enable biomarker-guided patient selection, optimal therapeutic sequencing and wider implementation of personalized treatment approaches.

***Anti-TSLP therapy: tezepelumab***

Tezepelumab is an monoclonal antibody targeting thymic stromal lymphopoietin (TSLP), a key regulator of the Th2 response involved in EoE. It acts on various immune cells, including dendritic cells, CD4+ and CD8+ T cells, granulocytes, and mast cells, promoting a feed-forward loop of inflammation[55]. A recent study showed increased TSLP receptor activity in oesophageal-derived memory CD4+ T cells from EoE patients, suggesting its critical role in disease pathogenesis. Tezepelumab, by blocking TSLP binding to its receptor, aims to modulate this pathway and has received FDA orphan drug designation for EoE[56]. A 52-week trial (NCT05583227) is currently investigating its safety and efficacy in adults and adolescents with EoE[57].

***Anti-Siglec-8 therapy: lirentelimab***

Lirentelimab (AK002) is a humanised IgG1 antibody targeting SIGLEC-8, a receptor present on mast cells, eosinophils, and basophils that plays a role in inflammation. It reduces mast cell activity and eosinophil counts through antibody-depend-

ent cellular cytotoxicity (ADCC) and apoptosis mechanisms[58]. In the ENIGMA trial, lirentelimab significantly improved symptoms and reduced eosinophils in patients with eosinophilic gastritis (EoG) and duodenitis (EoD), with those having concurrent eosinophilic oesophagitis (EoE) also showing improvement in dysphagia[59]. The KRYPTOS trial found that lirentelimab, at both high and low doses, led to significant histological remission (88%-92%) in EoE patients, though symptom improvement was not proportional[60]. A recent meta-analysis ranked lirentelimab 1 mg/kg as the most effective for histological remission, though it showed limited effects on endoscopic and symptomatic outcomes[61].

***Other monoclonal antibodies***

IL-15, an immune checkpoint released by dendritic cells, macrophages, fibroblasts, and epithelial cells, plays a key role in gut immunology and has been implicated in EoE pathogenesis, particularly in the basal layers of the epithelium during active disease[62]. CALY-002, an anti-IL-15 monoclonal antibody, is currently under investigation for its safety, pharmacokinetics, and pharmacodynamics in patients with EoE and coeliac disease (NCT04593251)[63]. Another trial, the EvolvE study, is assessing barzolvolimab (CDX-0159), a humanised mAb targeting KIT receptor tyrosine kinase, which is essential for mast cell survival and function in EoE (NCT05774184)[64, 65].

Previous treatments such as omalizumab (anti-IgE mAb) showed only a 33% improvement in histological and clinical outcomes in EoE patients, highlighting that EoE is not primarily IgE-mediated but associated with IgG4[66, 67]. Additionally, infliximab (anti-TNFα mAb) did not show significant improvements in EoE[68].

In summary, biologics such as dupilumab (an IL-4/IL-13 inhibitor) represent a major advancement in targeted therapy for EoE. These therapies focus on modulating the underlying immune response. However, challenges remain: 1. high costs and restricted access due to insurance limitations, limiting widespread clinical application, 2. uncertainty surrounding long-term immunomodulatory effects and the potential need for lifelong therapy, 3. variability in individual patient responses.

Novel biologic agents offer promising alternatives for treating EoE and other non-EoE eosinophilic gastrointestinal diseases, especially given the limited effectiveness of current medical and dietary treatments. However, the optimal dosage, duration, and long-term safety of these biologics remain unclear due to a lack of robust data. Future high-quality trials with standardized clinical assessments are needed to determine the ideal biologic dosage and identify the best patient populations for treatment.

## CONCLUSION

Current challenges in EoE pharmacotherapy include the complexity and heterogeneity of the disease, which makes treatment difficult to standardize. Despite advancements, the precise mechanisms driving EoE remain incompletely understood, complicating targeted therapies. PPIs, while widely accessible and commonly prescribed for EoE, show inconsistent efficacy, with only 30-50% of patients achieving histologic remission. Furthermore, PPIs do not target the underlying immune dysregulation of EoE, making them less effective as a standalone treatment. Although topical corticosteroids are highly effective, they are associated with high relapse rates once discontinued, with many patients experiencing a return of symptoms. To address gaps in EoE treatment and explore new strategies, numerous clinical trials on biologics for EoE and other eosinophilic gastrointestinal disorders are ongoing. In the last decade, molecular therapies for EoE have evolved from theoretical concepts to promising treatments undergoing phase 3 trials, with some likely becoming available soon. Anti-eosinophil therapies have demonstrated histologic improvements but often fail to alleviate symptoms, highlighting that eosinophils may not be the sole driver of disease. Furthermore, symptom improvement remains inconsistent across trials, suggesting that additional factors beyond eosinophils contribute to disease progression. Recent data on monoclonal antibodies, particularly dupilumab, show significant potential in managing EoE (Table 1). Emerging data on dupilumab's effect on esophageal distensibility suggests potential benefits even in fibrostenotic disease.

**Table 1.** Current monoclonal antibodies investigated for the therapy of eosinophilic esophagitis

| Monoclonal antibodies | Molecular mechanism | Study (reference) | Histologic remission | Endoscopic improvement | Clinical outcome | Active clinical trials |
|---|---|---|---|---|---|---|
| Dupilumab | IL-4R, IL-4, IL-13 | Dellon et al. (39) | Yes | Yes | Yes | NCT04394351 NCT05247866 |
| | | Dellon et al. (40) | Yes | Yes | Yes | |
| | | Hirano et al (36) | Yes | Yes | Yes | |
| Cendakimab | IL-13 | Hirano et al. (51) | Yes | Yes | Partial | NCT04753697 NCT05175332 NCT06101095 |
| Dectrekumab (QaX567) | IL-13 | Rothenberg et al. (54) | NS | - | NS | - |
| Mepolizumab | IL-5 | Dellon et al. (31) | NS | NS | NS | - |
| Reslizumab | IL-5 | Spergel et al. (30) | NS | - | NS | - |
| Benralizumab | IL-5-R | Rothenberg et al. (32) | Yes | Yes | NS | - |
| Tezepelumab | TSLP | - | - | - | - | NCT05583227 |
| Lirentelimab | SIGLEC-8 | Santos et al. (59) Jones et al. (60) | Yes | - | NS | - |
| CALLY-002 | IL-15 | - | - | - | - | NCT04593251 |
| Omalizumab | IgE | Loizou et al. (67) | NS | NS | NS | - |
| Barzolvolimab | KIT | - | - | - | - | NCT05774184 |
| Infilximab | TNF-a | Straumann et al. (68) | NS | NS | NS | - |

A key challenge will be integrating these therapies with existing treatments. Currently, PPIs, diet, or topical steroids might be offered to patients as first-line anti-inflammatory therapy (Figure 3). At present, there is no single strategy that has a clear advantage as the primary therapy for EoE, and, therefore, the choice of therapy needs to be individually discussed with the patients and their families. Molecular therapies may initially target patients unresponsive to PPIs, corticosteroids, or dietary elimination, or those with side effects or at risk for steroid complications. Factors such as accessibility, cost, effectiveness, safety, and patient response to traditional therapies will guide the use of molecular options. Future research should focus on optimizing treatment selection through biomarker-driven approaches, developing standardized formulations, and addressing access barriers to ensure that all patients benefit from effective pharmacotherapy. The integration of personalized medicine and innovative drug development will be crucial in refining EoE treatment strategies and improving patient quality of life.

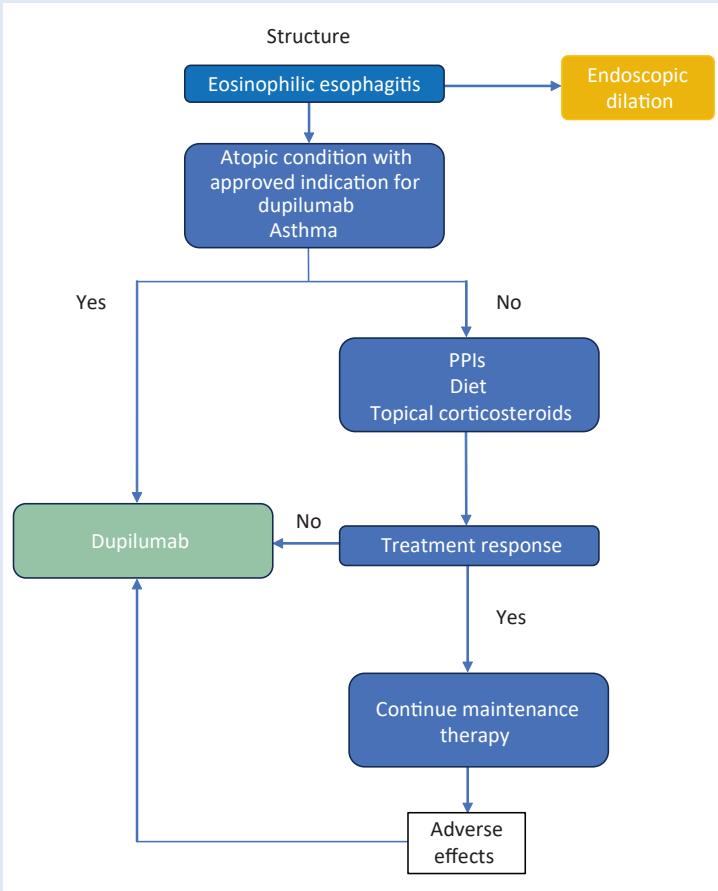


**Figure 3.** Therapeutic algorithm in eosinophilic esophagitis

**Conflicts of Interest:** Authors declare no conflicts of interest.

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