Abstract: Eosinophilic esophagitis is a chronic inflammatory condition that requires treatment to improve symptoms and prevent complications of esophageal remodeling, such as strictures and narrow-caliber esophagus. First-line treatments include proton pump inhibitors, topical corticosteroids, elimination or elemental diets, and esophageal dilation. Topical corticosteroids have typically required repurposing inhaled asthma medications by swallowing an aerosolized medication or mixing a nebulizer solution into a slurry. New topical corticosteroid formulations undergoing investigation include a premade budesonide oral suspension and disintegrating budesonide and fluticasone propionate tablets. The approach to an elimination diet is also changing, with an emphasis on patient preference when considering a traditional 6-food elimination diet compared with a step-up approach. This approach involves eliminating only 2 or 4 foods initially and expanding if necessary. While this method can be initially less effective for some patients, it generally involves fewer endoscopies and minimizes diet restriction. Beyond conventional therapies, a number of novel biologic agents are also under investigation. These include weekly subcutaneous injections or monthly intravenous infusions of RPC4046, dupilumab, antolimab, and benralizumab. The increasing number of approaches under development as well as anticipated submissions to the US Food and Drug Administration offer the potential of multiple specific therapies becoming available in the near future.
such as strictures and narrow-caliber esophagus. Response to therapy requires esophageal biopsies, as symptoms and histologic activity can vary independently. Nevertheless, the aims of EoE treatment are to improve symptoms and normalize the eosinophil count on histology. The US Food and Drug Administration has yet to approve any pharmacologic therapies for EoE. Current first-line treatments include off-label use of proton pump inhibitors (PPIs), topical corticosteroids repurposed from asthma formulations, elimination or elemental diets, and esophageal dilation. New and accelerated drug development now underway will likely lead to dramatic changes in EoE treatment regimens in the near future. This article discusses the current understanding of EoE treatments, with an emphasis on novel treatment options.

**First-Line Treatments With Novel Changes**

PPIs, topical corticosteroids, elimination or elemental diets, and esophageal dilation are well-established first-line treatments for EoE. For each of these treatments, there are new developments to consider (Figure).

**Proton Pump Inhibitors**

PPIs are commonly used in patients with EoE, with an estimated histologic response of 50.5% (95% CI, 42.2-58.7). Data are limited but have shown that adults on PPIs can remain in remission at 1-year follow-up. Data are limited but have shown that adults on PPIs can remain in remission at 1-year follow-up. 

EoE clinical practice guidelines have evolved. Previously, a PPI trial was required prior to making a diagnosis of EoE. However, new clinical practice guidelines suggest that PPIs should be viewed as a treatment option for EoE as opposed to a diagnostic tool. Widespread concerns have been raised by a number of observational studies regarding potential adverse events associated with PPIs. These adverse events include enteric infections, renal disease, dementia, and fractures. However, there are inherent limitations to observational studies, including the inability to infer causality. Moreover, a recent randomized clinical trial of cardiovascular and peripheral

![Image]

**Figure.** A flowchart of treatment options for patients with eosinophilic esophagitis. APT-1011, fluticasone orally disintegrating tablet; BOS, budesonide oral suspension; BOT, budesonide orodispersible tablet; PPI, proton pump inhibitor.

*a*In the appropriate context, esophageal dilation can be considered as well.

*b*Fluticasone 880 µg twice daily or budesonide 1 mg twice daily.

*c*Budesonide.
artery disease patients taking rivaroxaban, aspirin, or both who received pantoprazole or placebo for up to 3 years showed no increase in adverse events with PPIs except for a small increased risk of enteric infections.\textsuperscript{11} This study was not conducted in an EoE population and is limited to a 3-year follow-up, but it provides useful information and reassurance. Overall, PPIs are considered safe for long-term use in appropriately selected patients.\textsuperscript{12}

**Topical Corticosteroids**

Topical corticosteroids used for EoE to date have required off-label use of asthma preparations.\textsuperscript{2,4,13-15} These preparations include swallowing fluticasone propionate from a metered dose inhaler or creating a viscous slurry with aqueous budesonide and a thickener, such as sucralose, honey, or maple syrup. Clinicohistologic remission is seen in up to 68% of patients.\textsuperscript{16} Patients should be instructed on avoiding oral intake for 30 to 60 minutes afterwards and counseled that esophageal candidiasis is a complication seen in up to 20% of patients.\textsuperscript{3} While adrenal insufficiency has been reported in uncontrolled observational studies, randomized controlled studies have not supported the link between topical corticosteroids and adrenal insufficiency.\textsuperscript{17} Swallowed fluticasone propionate and budesonide slurries are considered comparable and are both acceptable choices, as shown in a recent 8-week randomized clinical trial of 129 adult and adolescent EoE patients receiving either fluticasone propionate 880 µg twice daily or budesonide 1 mg twice daily.\textsuperscript{18} Both of the topical corticosteroid regimens resulted in significant reductions in eosinophil counts and dysphagia scores from baseline, but there were no significant differences between the 2 groups. For example, remission of less than 15 eosinophils per high-power field (eos/hpf) occurred in 71% of patients taking budesonide and in 64% of patients taking fluticasone propionate ($P=.38$). Thus, fluticasone propionate and budesonide at these doses are comparable first-line choices for EoE if topical corticosteroids are chosen.

**Novel Topical Corticosteroid Formulations**

Several new topical corticosteroid formulations that enhance delivery to the esophagus and minimize patient burden of creating their own slurry are currently under investigation.\textsuperscript{19} These formulations include a budesonide orodispensible tablet (BOT; Dr. Falk Pharma GmbH), budesonide oral suspension (BOS; Shire), and a fluticasone propionate orally disintegrating tablet (APT-1011, Adare Pharmaceuticals; Table).

BOT has been shown to be safe as well as effective in reducing eosinophils and symptoms in adult patients. In a randomized clinical trial, 88 adult patients with active EoE were given BOT 1 mg twice daily vs placebo for 6 weeks.\textsuperscript{20} Clinicohistologic remission was defined as improvement in dysphagia score and a peak eosinophil count of less than 5 per hpf in 6 esophageal biopsies. Clinicohistologic remission was seen in 57.6% of patients receiving BOT compared with 0% in the placebo group ($P<.0001$). When treatment was extended to 12 weeks, the cumulative clinicohistologic remission increased to 84.7%. When examining histology on its own, 93% of patients receiving BOT achieved remission compared with 0% of patients receiving placebo. Symptomatic mild *Candida* rates were low (5%) in the BOT group, and all patients were successfully treated with an oral antifungal agent. Given its effectiveness, BOT was recently approved by the European Medicines Agency for treatment of EoE in adults.\textsuperscript{21}

BOS is a mucoadherent oral suspension that was specifically designed for EoE and is effective in improving symptoms and histology.\textsuperscript{22} This formulation was created after a randomized clinical trial demonstrated that a viscous budesonide slurry was more effective in improving histology than swallowed nebulized budesonide.\textsuperscript{23} To avoid the burden of patients mixing their own slurry, BOS was developed as a premade suspension. Initially, the formulation was assessed in a randomized clinical trial of 71 pediatric patients who were given placebo or BOS (either low, medium, or high dose).\textsuperscript{24} Of the patients receiving the medium dose (1.4 mg or 2 mg twice daily, depending on age), 52.6% achieved improvement in their symptom score and had an eosinophil count of less than 7 per hpf. BOS was then assessed in adolescents and adults.\textsuperscript{25} In a randomized clinical trial of 87 patients receiving BOS 2 mg twice daily or placebo for 12 weeks, there was a significant decrease in symptoms for patients receiving BOS compared with placebo. Moreover, 47% (23/49) of patients receiving BOS achieved 15 or less eos/hpf compared with 8% of patients receiving placebo ($P=.0001$). The histologic response in this study was below that seen with other topical corticosteroids, which may have been due to including a patient population with especially severe esophageal eosinophilia.

In a 24-week, open-label extension of the above study\textsuperscript{22} to assess long-term safety and tolerability, BOS was initiated in patients receiving placebo, whereas patients already receiving BOS had their dose halved to 2 mg daily.\textsuperscript{25} Forty-two percent of patients who had initially responded maintained histologic response in the open-label extension study. Moreover, all patients who had their dose escalated to 1.5 or 2 mg twice daily maintained histologic response. Overall, BOS was considered to be safe long term, and there was no evidence of adrenal insufficiency. Eleven percent of patients reported 1 or more treatment-emergent adverse events related to the study drug. The most commonly reported adverse events were...
NOVEL THERAPEUTIC APPROACHES TO EOSINOPHILIC ESOPHAGITIS

included respiratory disorders such as nasal congestion and asthma (10/82), nasopharyngitis (9/82), gastrointestinal symptoms such as pain and diarrhea (8/82), and candidiasis (6/82). The rate of candidiasis was consistent with prior data; up to 20% of patients receiving topical corticosteroids develop the condition.3 In a subset analysis, worsening of EoE was seen specifically in the patients who had their BOS dose reduced by 50%. 25 Mean peak eosinophil counts increased from the open-label extension baseline to week 24 in patients who had their BOS dose reduced from 2 mg twice daily to 2 mg daily (26.3 eos/hpf vs 75.2 eos/hpf; P= .033). A large phase 3 clinical trial of BOS has recently been completed, and results are awaited.26

Another topical corticosteroid under investigation is an orally disintegrating formulation of fluticasone propionate, APT-1011. In a randomized clinical trial, 22 patients with EoE received either placebo, 1.5 mg twice daily of APT-1011, or 3 mg daily of APT-1011 for 8 weeks.27 There was a significant reduction in symptoms in the group receiving 1.5 mg twice daily compared with placebo (P=.006). Moreover, eosinophil counts significantly improved with either dose of APT-1011; 75% of patients receiving 1.5 mg twice daily and 63% of patients receiving 3 mg daily had less than 15 eos/hpf at the end of treatment compared with 13% of patients receiving placebo. There was no significant difference between placebo and APT-1011 in terms of adverse events, and data to date suggest that systemic concentrations with this compound are low.39 A multicenter, phase 3 clinical trial of orally disintegrating fluticasone propionate is now underway.28

Dietary Approaches
Traditional dietary approaches have included either an elemental diet or a 6-food elimination diet (SFED), with new data supporting another option—a step-up elimination diet approach. An elemental diet involves the exclusive ingestion of an amino acid–based elemental formula and is histologically effective in up to 91% of patients.33,34 With strict avoidance, patients can have long-term histologic and clinical remission; up to 3 years has been described.33,34 In order to minimize endoscopy burden and the level of dietary restriction, novel approaches have been assessed, including a 4-food elimination diet (4-FED) and a 2-food

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Table. Novel Treatment Options for Eosinophilic Esophagitis

<table>
<thead>
<tr>
<th>Treatment Name</th>
<th>Dose</th>
<th>Study Phase</th>
<th>Symptom Response</th>
<th>Histologic Response</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOT</td>
<td>1 mg BID</td>
<td>3</td>
<td>+*</td>
<td>+</td>
<td>Orodispensible tablet, topical anti-inflammatory</td>
</tr>
<tr>
<td>BOS</td>
<td>2 mg QD or BID</td>
<td>2</td>
<td>+</td>
<td>+</td>
<td>Premade oral suspension, topical anti-inflammatory</td>
</tr>
<tr>
<td>APT-1011</td>
<td>1.5 mg BID or 3 mg QD</td>
<td>1/2a</td>
<td>+</td>
<td>+</td>
<td>Orally disintegrating tablet, topical anti-inflammatory</td>
</tr>
<tr>
<td>RPC4046</td>
<td>180 or 360 mg weekly</td>
<td>2</td>
<td>Unclear</td>
<td>+</td>
<td>IL-13 monoclonal antibody, subcutaneous injection</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>300 mg weekly</td>
<td>2</td>
<td>+</td>
<td>+</td>
<td>IL-4 receptor alpha component of type 2 receptor monoclonal antibody (blocks IL-4 and IL-13), subcutaneous injection</td>
</tr>
<tr>
<td>Antolimab</td>
<td>0.3-3.0 mg/kg monthly</td>
<td>2</td>
<td>+</td>
<td>+</td>
<td>Siglec-8 monoclonal antibody (eosinophil apoptosis, inhibits mast cell activation), intravenous infusion</td>
</tr>
<tr>
<td>Benralizumab</td>
<td>30 mg weekly</td>
<td>2</td>
<td>Unknown</td>
<td>Unknown</td>
<td>IL-5 receptor alpha monoclonal antibody (depletes eosinophils), subcutaneous injection</td>
</tr>
</tbody>
</table>

APT-1011, fluticasone orally disintegrating tablet; BID, twice daily; BOS, budesonide oral suspension; BOT, budesonide orodispensible tablet; IL, interleukin; QD, once daily; Siglec-8, sialic acid–binding immunoglobulin-like lectin 8.

*All plus signs indicate a positive response.

With 600-mg loading dose.

Studied in an eosinophilic gastritis and gastroenteritis patient population.
elimination diet (2-FED) with a step-up approach. A step-up approach is a reasonable option given that predominant triggers are milk and wheat, and up to 75% of patients undergoing the SFED only have 1 or 2 food triggers.

A 4-FED involves avoiding dairy products (including cow, goat, and sheep milk), gluten-containing grains, eggs, and legumes. In a prospective, multicenter study, 52 adolescent and adult patients underwent 6 weeks of 4-FED. The primary outcome was clinicohistologic remission, defined as a decrease of at least 50% of the baseline dysphagia symptom score and less than 15 eos/hpf in esophageal biopsies. After 6 weeks, patients in remission underwent systematic food reintroduction every 6 weeks accompanied by EGD with biopsies. Nonresponders were offered the SFED with subsequent food reintroduction. Clinicohistologic remission with the 4-FED was achieved in 54% of patients. A similar response rate was seen in a multicenter study of 78 children.

A 2-FED involving the elimination of dairy products and wheat (including gluten-containing grains) for 6 weeks followed by EGD with biopsies has been studied in 130 adolescent and adult patients. Nonresponders were offered 4-FED for 6 weeks, and, if still nonresponsive, were offered SFED for 6 weeks. When patients achieved clinicohistologic remission, they underwent individual food reintroduction with EGD and biopsies in 6-week intervals. The 2-FED achieved symptom improvement and histologic remission in 43% of patients, with no difference between age groups. For nonresponders, the subsequent 4-FED and SFED achieved remission in 60% and 79% of patients, respectively. Both the 2-FED and the 4-FED have the advantages of lower endoscopic burden to assess response and less dietary restrictions with inherent adherence issues when compared to the conventional SFED. A survey of 42 patients found that only 57% were adherent with SFED. In general, shared decision-making with an emphasis on patient preference is essential when embarking on a dietary approach. This includes discussing patient confidence in maintaining an elimination diet and the patient’s opinions on the number of endoscopies he or she is willing to undergo.

**Esophageal Dilation**

There are 3 phenotypes to EoE—fibrostenotic (rings and strictures), inflammatory (exudates and linear furrows), and mixed. The fibrostenotic and mixed phenotypes often require esophageal dilation. Previously, there were concerns regarding increased complication rates with esophageal dilation for EoE, but in a recent meta-analysis, clinical improvement occurred in 95% of patients, with major complications seen in less than 1%. In this meta-analysis, the perforation rate was 0.38% and the hemorrhage rate was 0.05%. These rates are similar to those reported for all patients who are dilated (0.1%-0.4%). As such, esophageal dilation is a safe approach for EoE patients. Ultimately, controlling esophageal inflammation with medications or diet is paramount, and recent research suggests that this will lead to a decreased need for esophageal dilation.

**Biologic Agents**

There are multiple new biologic agents to treat EoE now in various stages of development, including RPC4046 (Receptos), dupilumab (Dupixent, Regeneron Pharmaceuticals and Sanofi), antolimab (previously AK002, Allosk), and benralizumab (Fasenra, AstraZeneca; Table).

Interleukin (IL) 13 is overexpressed in the esophageal mucosa of EoE patients and is involved in eosinophil recruitment, remodeling, and fibrosis. RPC4046 is a humanized monoclonal antibody against IL-13 that has been evaluated as a potential therapeutic agent in EoE. In a pilot study of 23 adult patients, an infusion of an IL-13 antibody reduced esophageal eosinophil counts and EoE-related gene expression. Given these preliminary data, a weekly subcutaneous injectable form of RPC4046 was evaluated in a phase 2 trial. This multicenter study of 99 adults with active EoE randomized patients to either placebo, low-dose RPC4046 (180 mg), or high-dose RPC4046 (360 mg) weekly for 16 weeks. At the end of the study, 50% of patients receiving either dose of RPC4046 achieved histologic remission of less than 15 eos/hpf compared with 0% of patients receiving placebo (P<.001). There was no significant difference in symptom scores between the treatment and placebo groups, but the study was not powered sufficiently to assess this outcome. In a subgroup analysis of the corticosteroid-refractory patients enrolled in this trial, patients receiving either dose of RPC4046 had a significant reduction in their eosinophil counts compared with patients receiving placebo (P<.0001), suggesting promise for this challenging patient population. Mild adverse events were seen with similar frequency in both groups receiving treatment and placebo, and included headache, upper respiratory tract infection, arthralgias, diarrhea, and nausea. Additional larger phase 3 trials are needed for this compound in order to further elucidate its potential role in EoE management.

Dupilumab is a fully human monoclonal antibody directed against the IL-4 receptor alpha component that inhibits signaling of both IL-4 and IL-13, which are key initiators of type 2 inflammation. Dupilumab has previously been shown to be effective and safe in atopic dermatitis, asthma, and chronic sinusitis with nasal polyposis. In a recent multicenter clinical trial, EoE patients received subcutaneous injections of either placebo or dupilumab...
with a loading dose of 600 mg and then 300 mg weekly for 12 weeks.\textsuperscript{53} Of patients receiving dupilumab, 83% achieved an eosinophil count of less than 15 per hpf at week 12 compared with 0% receiving placebo (\textit{P}<.0001). Thirty-nine percent of patients receiving dupilumab had symptomatic improvement by week 10 compared with 13% receiving placebo (\textit{P}=0.049). Interestingly, esophageal distensibility was also significantly improved with dupilumab compared with placebo at week 12. Mean percent change from baseline was -6.2% with placebo and 11.8% with dupilumab (\textit{P}<.0001). Dupilumab was well tolerated with no serious adverse events or deaths. The most common side effects were injection site erythema (35% in the dupilumab group vs 8% in the placebo group) and nasopharyngitis (17% in the dupilumab group vs 4% in the placebo group). A large phase 3 trial is underway to further assess the efficacy of dupilumab.\textsuperscript{54}

Antolimab, administered as a monthly infusion, is an antibody to sialic acid–binding immunoglobulin-like lectin 8 (Siglec-8). Siglec-8 is a surface receptor found selectively on human eosinophils and mast cells, both of which are elevated in EoE.\textsuperscript{55,56} Binding of a monoclonal antibody to Siglec-8 induces apoptosis of activated eosinophils and inhibits mast cell activation.\textsuperscript{56-59} The compound was well tolerated and improved symptoms in small studies of 29 patients with allergic conjunctivitis and 47 patients with chronic urticaria.\textsuperscript{60,61} Antolimab has also demonstrated improvement in symptoms and histology in patients with eosinophilic gastritis and gastroenteritis in the ENIGMA trial, a randomized clinical trial of 59 adult patients receiving high-dose antolimab (0.3-3.0 mg/kg), low-dose antolimab (0.3-1.0 mg/kg), or placebo for 4 months.\textsuperscript{62} The antolimab groups had an overall 95% mean reduction in tissue eosinophils relative to their baseline compared with a mean increase of 10% in the placebo group (\textit{P}<.0001). Histologic remission, defined as 6 or less eos/hpf, was seen in 95% (37/39) of patients receiving treatment. In a subgroup analysis, 93% (13/14) with concomitant EoE had histologic remission. The most common adverse event was a mild to moderate infusion reaction that occurred more frequently in the first infusion only. Antolimab is currently undergoing a phase 2/3 trial with a larger group of patients with EoE.\textsuperscript{53}

Benralizumab is an emerging therapy that has improved histology in a small cohort of patients.\textsuperscript{64} It is a monoclonal antibody against IL-5 receptor alpha, which enhances antibody-dependent cellular cytotoxicity and depletes eosinophils. It has been effective in decreasing eosinophils in patients with asthma and platelet-derived growth factor receptor alpha (PDGFRA)-negative hypereosinophilic syndrome.\textsuperscript{64-66} In a subgroup analysis of PDGFRA-negative hypereosinophilic syndrome patients, 2 had active EoE.\textsuperscript{64} All patients received 30 mg of benralizumab subcutaneously every 4 weeks. At 24 weeks follow-up, biopsies showed no eosinophils. Benralizumab is currently undergoing assessment in EoE patients, but no data are available to date.

**Conclusion**

EoE is a prevalent condition that leads to esophageal remodeling when left untreated. First-line treatments include PPIs, topical corticosteroids repurposed from asthma medications, dietary interventions, and esophageal dilation. Efficacy ranges from approximately 50% to 70%, meaning that some patients will need to be treated with more than 1 treatment approach. Fortunately, there are many new therapies on the horizon. Several specific EoE formulations of topical corticosteroids are now under study to improve esophageal delivery. There are also a number of monoclonal antibodies undergoing clinical trials that may offer the potential for more targeted therapy with less frequent dosing. In the near future, there will likely be an increasing number of compounds submitted to the US Food and Drug Administration specifically for the therapy of EoE.

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