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Management of refractory eosinophilic oesophagitis

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Abstract

The goal of this Review is to discuss the clinical approach to patients who do not respond to treatment for eosinophilic oesophagitis (EoE). Refractory EoE is challenging to manage as there are limited data to guide decision-making. In this Review, refractory EoE is defined as persistent eosinophilia in the setting of incomplete resolution of the primary presenting symptoms and incomplete resolution of endoscopic findings following a PPI trial, and after treatment with either topical steroids or dietary elimination. However, this definition is controversial. This Review will examine these controversies, explore how frequently non-response is observed, and highlight potential explanations and predictors of non-response. Non-response is common and affects a large proportion of patients with EoE. It is important to systematically assess multiple possible causes of non-response, as well as consider treatment complications and an incorrect diagnosis of EoE. If non-response is confirmed, second-line treatments are required. Although the overall response rate for second-line therapy is disappointing, with only half of patients eventually responding, there are several promising agents that are currently under investigation, and the future is bright for new treatment modalities for refractory EoE.

Eosinophilic oesophagitis (EoE) is a chronic allergic immune-mediated clinicopathological condition in which an oesophageal eosinophil infiltrate causes symptoms of oesophageal dysfunction[1]. EoE was first described in the late 1970s[2,3], and the condition as it is recognized today was reported in a series of publications in the early 1990s[4–6]. Since the publication of these reports, there has been a rapid increase in both the incidence and prevalence of EoE, which has outpaced the increase in awareness of the condition[7,8]. Although EoE is a worldwide disease, its prevalence is highest (~1 in 2,000 people) in the USA, Western Europe and Australia, and its current incidence is estimated to be 10 cases per 100,000 individuals per year[7,9,10]. EoE represents a major cause of upper gastrointestinal morbidity in patients of any age, but is more common in children and young adults. Accordingly, it has become the second most common cause of oesophagitis[7,11], the most

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Competing interests statement

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common cause of food bolus impaction[12,13] and is seen in up to 23% of patients who undergo upper endoscopy for symptoms of dysphagia[14–17]. Annual costs related to EoE in the USA alone are estimated to be ~US$1 billon per year[18].

To diagnose EoE, patients must present with symptoms of oesophageal dysfunction and an oesophageal biopsy with at least 15 eosinophils per high-power microscopy field (eos/hpf)[19–21]. Symptoms of EoE include dysphagia, food impaction, heartburn and chest pain; abdominal pain, vomiting and poor growth can be manifestations in children. However, other local and systemic secondary causes of eosinophilia must be excluded, and eosinophilia must persist after a high-dose trial of a PPI[20]. Although current guidelines suggest that after a PPI trial treatment for EoE can comprise either topical corticosteroid or dietary elimination therapy, there are currently no FDA-approved treatments for EoE[19,20,22]. Topical corticosteroids that are asthma preparations, such as fluticasone or budesonide, can be swallowed rather than inhaled to coat the oesophagus and provide an anti-inflammatory effect. Dietary elimination removes potential food triggers, and can be directed either by allergy testing or empirically. In some cases, a hypoallergenic elemental formula composed of amino acid solids, simple carbohydrates and medium-chain triglycerides can also be used.

The goal of this Review is to discuss the clinical approach to patients with EoE who do not respond or are refractory to treatment. The definition of refractory EoE will be discussed first, as well as controversies related to this definition. Second, the frequency of non-response will be explored and potential explanations and predictors of non-response will be highlighted. Last, the evidence base for second-line treatments in EoE will be reviewed and emerging therapeutic options will be discussed.

What is refractory EoE?

From a conceptual standpoint, refractory EoE can be defined as ongoing symptoms, abnormal endoscopic findings (FIG. 1) and persistent oesophageal eosinophilia after a PPI trial and after treatment with either topical steroids or dietary elimination therapy. Notably, this definition does not perfectly parallel the diagnostic criteria, which do not require endoscopic findings[19,20]. In addition, for the purposes of this Review, PPIs remain within the diagnostic algorithm for EoE and are not considered as treatment modalities. However, it is important to acknowledge that the role of PPIs in oesophageal eosinophilia and EoE is an area of ongoing controversy and has a rapidly evolving evidence base. In patients who have an EoE clinical phenotype, there is increasing recognition that individuals who respond to PPI treatment (PPI-responsive oesophageal eosinophilia; PPI-REE) are similar in almost all aspects of the disease to those who do not respond (classically defined as EoE)[14,23–27]. A systematic review and meta-analysis that was published in 2016 showed that ~50% of such patients with oesophageal eosinophilia responded to PPI therapy[28]. Moreover, other studies have identified novel acid-independent anti-eosinophil properties of PPIs that can mechanistically explain the pharmacological response to this class of medications[29,30]. Consequently, the question remains as to whether PPIs should be considered for the treatment of EoE, rather than solely as a diagnostic test; however, guidelines have not yet changed to reflect this aspect[31]. Thus, it would be difficult to consider a patient who does not respond to a PPI trial to have refractory EoE without that patient also failing to respond

to either topical steroids or dietary elimination. This nuance has been reflected in the earlier conceptual definition of refractory EoE.

Application of the definition of refractory EoE in clinical practice can be challenging. Current guidelines do not discuss this issue in depth[20] and there are limited studies published specifically on this topic[32–35]. In addition, each clinicopathological component of EoE has to be considered when assessing response[36]. For example, it is unclear as to what threshold constitutes true symptom non-response, and whether non-response should be solely defined as no change in symptoms, <50% decrease in symptoms, or some other threshold. Although there are now several validated symptom and quality of life measures for use in EoE[37–42], these measures are not typically used in clinical practice as they can be somewhat time-consuming, and were initially developed as research tools and have an undefined response threshold. Similarly, it is unclear as to what constitutes histological non-response — potential criteria include failure to normalize a biopsy sample with any number of persistent eosinophils, failure to achieve a set percentage decrease in eosinophil count or failure to lower the eosinophil count past a pre-specified threshold. The same issue remains in regard to endoscopic findings. It is unclear whether endoscopic non-response requires the complete normalization of the appearance of the oesophagus, a pre-defined improvement in a validated endoscopic severity measure (such as the EoE Endoscopic Reference Score (EREFS))[43], or any improvement in a measure such as this. As discussed later, there is also the possibility for response in one domain (that is, symptoms) and not in another (that is, histology or endoscopy).

Owing to the lack of data to guide this definition, and for the purpose of this Review, refractory EoE will be defined as persistent eosinophilia in ≥15 eos/hpf in the setting of incomplete resolution of the primary presenting symptoms and endoscopic findings (BOX 1).As discussed later in this Review, the histological response threshold for EoE is often empirically chosen and varies markedly between studies[22]. However, in the past few years there have been both retrospective and preliminary prospective data showing that a response threshold of 15 eos/hpf is associated with improved symptomatic and endoscopic responses, and that lowering this threshold to less than 15 eos/hpf does not result in a substantial additional symptom or endoscopy response[44,45]. Moreover, failure to reach this threshold has also been associated with an increased need for oesophageal dilation in patients who have EoE that is complicated by strictures or narrowing[46]. These emerging data lend some credibility to 15 eos/hpf being a reasonable response threshold, and this level provides symmetry with the diagnostic criteria. Nevertheless, the response threshold must be individualized in clinical practice. For example, a patient who has 200 eos/hpf at baseline and achieves a post-treatment eosinophil count of 16 eos/hpf, as well as symptomatic and endoscopic improvement, could be considered to be a responder. Conversely, a patient who progresses from 20 eos/hpf to 14 eos/hpf after treatment, with persistent symptoms and endoscopic findings, could be classified as a non-responder. Importantly, eosinophil counts (eos/hpf) will vary with the size of the high-power microscopy field used and, therefore, a more accurate method is to determine eosinophil density per unit area (eos/mm^2)[47]. As this method is not yet frequently carried out in clinical practice, it is important to confirm that the size of the hpf used to assess eosinophil infiltrate post-treatment is identical to that used for the pre-treatment determination. For reference, a count of 15 eos/hpf is equivalent to ~60

eos/mm^2 for common microscope field areas in the 0.24–0.3 mm^2 range. Moreover, long-term outcome data are required concerning the clinical, endoscopic and histological consequences of persistent low-level oesophageal eosinophilia over time to more fully inform histological response thresholds. This information would also complement data showing that eosinophilia and diagnostic delay are associated with increased risk of strictures and fibrostenotic phenotypes[48–50].

How common is non-response?

Data concerning the frequency of non-response can be obtained from several sources, including case series, cohort studies, randomized controlled trials (RCTs) and meta-analyses. To date, there have been 12 RCTs that have examined response to topical corticosteroids in EoE[51–62]. With the exception of one study that evaluated a novel experimental budesonide formulation in which non-response occurred in 0–6% of patients[59], the majority of studies showed histological non-response[51–58,60–62]. The frequency of non-response varied depending on the eos/hpf threshold used: non-response was reported in 6–85% of individuals using the most stringent histological threshold reported for that specific study, and in 22–69% of individuals using a response threshold of <15 eos/hpf (TABLE 1). In these studies, symptoms and endoscopic findings were not consistently evaluated, and validated measures have only been used in one new study[60]; therefore, it is difficult to determine exact symptomatic and endoscopic non-response rates (TABLE 1). Owing to the rigorous design and patient follow-up in RCTs, these results are probably the best that can be expected. Indeed, in the few large cohort studies that have been reported with real-world experience, non-response has been even more commonly reported. For example, Wolf and colleagues[32] reported a 43% histological non-response rate using a threshold of <15 eos/hpf, Moawad and colleagues[63] reported a 63% non-response rate (5 eos/hpf) in preliminary data and Leung and colleagues[33] reported a 44% non-response rate (10 eos/hpf). However, these high non-response rates are not universal. Philpott and colleagues[64] reported 8% non-response using a threshold of <5 eos/hpf, Boldorini and colleagues[65] reported 24% non-response (≤6 eos/hpf) and Henderson and colleagues[66] reported 19% (15 eos/hpf).

Although there are currently no published RCTs that evaluated dietary elimination therapy in EoE, there are several prospective and retrospective cohort studies that investigated this modality[6,64,66–78], and summary data for non-response has been compiled in a meta-analysis[79].This study found that elemental formula was the most effective treatment for EoE, with only a 9% non-response rate. The six-food elimination diet (SFED; typically with the elimination of dairy, wheat, egg, soy, nuts and seafood) had a non-response rate of 28% and targeted (allergy-directed) elimination had a non-response of 55%. However, there are studies of SFED in which non-response rates almost reach 50%[64,74].

In summary, data for both pharmacological and dietary treatment modalities for EoE show that a large minority, and sometimes up to half, of patients with EoE will not respond to initial treatment. This aspect highlights a substantial unmet need in the therapeutic approach to these patients, and shows that non-response will commonly be encountered in clinical practice.

Evaluation and causes of non-response

Before deciding on a second-line treatment plan for patients with EoE, it is imperative to systematically consider the potential reasons for why a patient might have not responded to first-line therapy. As will be discussed below, there are multiple specific and identifiable causes of non-response, which if corrected could lead to response. Thus, it is important to not label a patient as non-responsive until these issues are investigated.

Symptom and histology discordance

First, the clinician must ask which component of the disease presentation has not improved. When a patient has persistent symptoms, endoscopic findings and oesophageal eosinophilia, there is probably true non-response. However, when there is discordance between some of these features, additional investigation is necessary. This discordant response can occur because of the separate inflammatory and fibrostenotic aspects of EoE[49,80]. The inflammatory component of EoE relates to local consequences of eosinophilia and manifests with tissue injury and endoscopic findings of oedema, linear furrows and white plaques. By contrast, the fibrostenotic component relates to oesophageal remodelling that results in oesophageal strictures or narrowing. An anti-inflammatory treatment, such as dietary elimination or topical steroids, can improve the histological findings, but symptoms of dysphagia can persist if there is an oesophageal stricture. Similarly, symptoms of heartburn, dysphagia or odynophagia can persist despite a histological response if there is a treatment complication, such as candidal oesophagitis or herpes oesophagitis. By contrast, symptoms can improve despite ongoing eosinophilia in several instances: if a stricture has been dilated, if a patient modifies his or her diet enough to mitigate symptoms (in the most extreme example, a person using a liquid-only diet would have no symptoms of dysphagia), or with regression to the mean. Furthermore, when assessing endoscopic findings of EoE, it is important to fully insufflate the oesophagus, take adequate time to assess multiple potential findings (including subtle findings, such as oedema or narrowing), and use a validated metric, such as the EoE EREFS, which also has an atlas of endoscopic images that can be used for reference[43]. The features of the EREFS that are considered inflammatory (oedema, exudates and furrows) might have a better response to anti-inflammatory or anti-eosinophil-directed therapy than the fibrostenotic features (rings and strictures). However, given the fact that fibrostenotic features can sometimes improve after treatment, a full assessment of all endoscopic signs is warranted[81]. As symptom and endoscopic or histological discordance seems to be a common feature of EoE[36,82], all of these issues should be considered before proceeding with second-line treatments.

Non-response to topical steroids

Several factors underlie non-response to topical steroids[34] (BOX 2). The first is adherence; not only must the patient take the medication but they must take the medication in the correct manner to maximize oesophageal deposition. For topical steroids, this adherence requires that they swallow the medication and refrain from eating or drinking for 30–60 min following ingestion. As there are no FDA-approved oesophageal-specific medications for EoE, clinicians currently rely on patients to correctly spray a multi-dose inhaler into their mouth or mix a viscous solution of budesonide correctly. If the oesophageal dwell time is

too low, then the medication might be ineffective[55,83]. Given promising results of new oesophageal-specific formulations, a large proportion of non-response might eventually be attributed to poor oesophageal delivery[58,59]. In addition, as these medications are expensive and it can be difficult to obtain insurance or healthcare provider approval for them, some patients do not obtain their prescription medications owing to high cost. If non-adherence is noted, a discussion about the reason — cost, current adverse effects, concern about the long-term adverse effects, dosing frequency, preference for another treatment, lack of perceived effect on symptoms, and so on — should take place. Patients must also take the correct dose of the medication. The recommended dose of fluticasone is 440–880 μg per day in younger children and 880–1,760 μg per day in older children and adults, and the dose of budesonide is 1 mg per day in younger children and 2 mg per day in older children and adults[20–22]. However, for both medications it seems that doses at the higher end of these ranges are most effective[52,56–59]. Nevertheless, because these are unconventional medications, some patients and practitioners can be confused about the dosing and the route of administration; therefore, a carefully collated history regarding adherence is necessary to investigate this. As noted earlier, the topical use of steroids can be complicated by candidal or herpes oesophagitis[53,55,56,84,85], which gives the impression that symptoms have not improved. Symptoms can also persist if there is an oesophageal stricture or narrowing that has not been recognized or dilated. Furthermore, there might be persistent food or environmental allergen exposure, associated allergic diseases that cause steroid non-response[86] or it could be possible that patients might have a steroid-insensitive subtype of EoE.

Non-response to dietary elimination

There are also causes of non-response to dietary elimination (BOX 2). For dietary elimination, adherence is particularly crucial, and given the complexities of some of the dietary elimination treatment options, it is understandable that patients might not be able to fully comply. Moreover, the increased costs that are associated with these speciality diets[87] could also affect adherence. In addition, if a patient and their clinician are not working with a dietician or nutritionist who has EoE-specific knowledge, dietary treatment is much less likely to be effective[88–90]. Under these circumstances, lack of adherence would be directly related to a lack of EoE-specific knowledge; for example, in a patient who does not know that whey protein is derived from dairy and uses it as a supplemental protein source. In patients for whom non-adherence to dietary treatment is identified, it is important to have a detailed discussion with the patient about the reasons. Considerations can include that they are overwhelmed with the dietary restrictions, they need additional nutritional resources and support, they cannot afford speciality foods, they are unable to incorporate dietary restrictions into their current family or work lifestyle, they do not see any positive results on symptoms, or they feel reluctant to admit that it is not a desirable treatment for them. Once the underlying reasons are identified, they can potentially be addressed. A further consideration can be inadvertent cross-contamination, which can occur even with very careful patients who adhere to their dietary regi-men; however, there is limited data regarding the minimal amount of a food allergen that is required to trigger EoE. An additional cause of dietary non-response is that the true trigger for EoE in a patient is not included in the elimination diet. The existing allergy testing modalities of skin-prick testing and serum food-specific IgE testing do not provide high accuracy for the identification of

food triggers in EoE[91]. Two separate prospective studies of SFED with subsequent food re-introduction in dietary responders found only a 13% concordance between skin-prick testing and the identifying trigger foods in EoE[71,72], with an additional study published in 2016 confirming this discordance[92]. Atopy patch testing (APT) has shown some promise in being more accurate than skin-prick testing for identifying food triggers in EoE[68], but has not been a reproducible technique[66]. Conceivably, a patient can be perfectly compliant with their prescribed diet, but might still not respond as there are unidentified food triggers that have not been eliminated.

Other reasons for non-response

If a patient does not respond to therapy as expected, it is important to reconsider the diagnosis of EoE. To this end, ensuring that the patient meets the consensus diagnostic guidelines for EoE is crucial, including non-response to a high-dose PPI trial[19,20]. In some cases, the original pathology slides must be re-examined to reaffirm that there were increased levels of oesophageal eosinophilia. If there are persistent symptoms, it is also important to determine whether these are due to EoE or whether there might be another cause. In particular, overlapping reflux disease, an oesophageal motility disorder, or a functional condition should be considered. Studies have shown that eosinophils can cause oesophageal hypersensitivity that can persist even with resolution of eosinophilia[93] and can be associated with functional dyspepsia[94].

Predictors of non-response

Limited data exist from studies that investigated predictors of non-response in EoE and most are related to topical steroids. In two separate retrospective cohort studies that used multivariate analyses of several clinical, endoscopic and histological features of EoE, only oesophageal dilation at the baseline endoscopy (before treatment) was associated with non-response, although the reasons for this association are unclear[32,63]. In one of these studies, increased levels of mast cells and eotaxin-3 in oesophageal tissues were associated with improved response rates[32]; however, this finding conflicts with another study that demonstrated that high levels of mast cells were associated with non-response[65]. Levels of phosphorylated extracellular signal-regulated kinase (ERK) were also shown to be increased in steroid-refractory patients[95]. In a RCT of fluticasone versus placebo, pre-treatment gene expression for histological non-responders compared with responders was assessed[57]. The results suggested that several genes might be differentially expressed before treatment in non-responders. Although these data hold promise for potentially individualizing treatment in the future, the finding must be independently replicated in a larger cohort of patients. Preliminary data regarding a polymorphism in the promoter of transforming growth factor β1 (*TGFB1*) have shown that a CC genotype is associated with favourable treatment response in children with EoE[96].

A treatment-resistant EoE phenotype has been described[97]. Patients with extreme narrow-calibre oesophagus, defined by diffuse narrowing or severe stricturing that precluded passage of a standard adult upper endoscope (8–10 mm in diameter), were approximately one-third less likely to respond to topical steroids than patients without these fibrostenotic

changes. This extreme narrow-calibre oesophagus phenotype was observed in 9% of cases of EoE, and the mechanisms of non-response in this group have yet to be elucidated. However, another study linked severe oesophageal rings in patients with EoE to decreased oesophageal compliance, as measured by an endoluminal functional luminal imaging probe[98], which suggests that a transmural fibrotic process might occur[99]. Conceivably, the topical administration of medication would be insufficient in these cases, but this aspect remains to be examined. Despite data assessing predictors of response, there are studies in which no predictors have been identified[54,100], which warrants substantially more work on this topic. In addition, given promising results and high response rates with new oesophageal-specific medication formulations[58,59], it is possible that a strong predictor of non-response to topical steroids could be low oesophageal dwell time[55].

Treatment options for non-responders

After excluding issues that are related to patient adherence, dosing, formulation or medication administration, ongoing exposure to allergens or food triggers, and knowledge related to dietary elimination, a patient who has EoE can be confirmed as a non-responder. At this stage, the clinician must then determine the next best option for treatment. Unfortunately, there are few data to guide this process. A suggested algorithm that is based on the existing data, clinical experience and current guidelines is presented in FIG. 2, the principle of which is to identify treatment options in a logical and stepwise manner. If there is continued non-response after treatment with standard first-line therapies for EoE, then there are several potential second-line agents that could be used, but each of these has limitations. However, data describing the success rates of second-line therapies are limited. One study that investigated this issue specifically found that only 48% of initial non-responders would proceed to have a response with second-line agents[32]. In another report, 54% of patients who were refractory to standard first-line EoE treatment responded to therapy with second-line agents[33]. Owing to this low response, patients who are refractory to standard EoE treatments should be considered for clinical trials, in which some novel compounds are under study. The next section will review the existing data for several potential second-line treatment options for EoE. Although these therapies are discussed individually and the algorithm suggests that these should be used separately, the clinical benefit of combination therapy for EoE is unknown. However, in certain patients, combination therapy might be worth considering if individual treatment options are ineffective.

Topical steroids

For topical steroids, data suggest that a higher dose of oral viscous budesonide is associated with improved histological response. In an RCT of a new budesonide suspension in children with EoE, a high-dose arm (2.8–4 mg per day, depending on age) had a 94% histological response rate (≤6 eos/hpf) compared with the low-dose arm (0.35–0.5 mg per day, depending on age), for whom there was a 24% response[58]. In addition, RCTs that use fluticasone at high doses (1,760 μg per day[52,57]) tend to have better response rates than lower doses, such as 880 μg per day[51], but there are no published trials that specifically investigate dose–response for fluticasone.

In addition to budesonide and fluticasone, other topical steroids, including beclomethasone, mometasone and ciclesonide, have been shown to be effective[101–103]. Ciclesonide is of particular interest, as this drug is a highly potent steroid that must be activated by an esterase, which is a hydrolase enzyme that is present in both the lungs and oesophagus[103]. A case series of four patients who had prior steroid failure showed that ciclesonide might be a promising agent[103], but the results were not replicated in two other small series of patients[32,104].

As oesophageal medication deposition and increased contact or dwell time have been associated with histological responses in EoE[55], there is an active interest in developing oesophageal-specific formulations of topical steroids. A phase II study of a budesonide effervescent tablet showed rates of 95–100% histological response (<16 eos/mm^2) in adults, as well as an improvement in endoscopic severity, but did not show a symptom improvement compared with placebo[59]. In addition, a phase II study of a mucoadherent budesonide oral solution had a 39% rate of histological response (≤6 eos/hpf), with associated improvements in endoscopic severity and the severity and frequency of dysphagia symptoms[60]. Both agents are currently in phase III studies. However, as there are no FDA-approved topical steroids for EoE, patients and physicians must adapt the medications that are currently available to maximize oesophageal deposition. Although the original formulation of oral viscous budesonide comprised aqueous budesonide respules with sucralose[105,106], data now show that mixing aqueous budesonide with elemental formula, honey, powdered drink mixes, xanthan gum, or having it compounded in a speciality pharmacy, can also be effective[83,107]. For fluticasone, there is a preliminary report that showed that it is effective to open the diskus dry powder inhaler device and ingest the fluticasone powder directly[108]. Nevertheless, these unconventional approaches highlight the need for specifically developed oesophageal formulations for EoE that might increase the response rate to topical steroids.

Elemental formula

When empirical or allergy test-directed elimination diets are unsuccessful, the use of an elemental formula can be highly effective. Elemental formula was one of the first treatments to be used for EoE[6], and the high rates of response in children (>90–95%) helped to confirm that EoE was an allergic disorder[69,75,76]. These hypoallergenic formulas are composed of amino acid solids, simple carbohydrates and medium-chain triglycerides, and rapidly lead to histological and symptomatic improvement if taken as the sole source of nutrition. The efficacy of these diets was initially demonstrated in children but has also been shown in adults[77,78]. Although effective, there can be several downsides to this treatment. First, a formula diet is not an issue in infants and young children, but is more difficult to maintain as a long-term treatment in older children, adolescents and adults. Second, historically, these formulas have not been palatable, and although that is changing, some patients cannot tolerate the flavour or the volume required and must use a feeding tube to maintain adequate nutrition. This feeding approach is a particular issue for adults who are accustomed to eating solid food; in one study, more than one-third of patients withdrew because they could not tolerate the formula[77]. Third, these formulas are expensive and might be difficult to secure through healthcare systems. Last, the goal of this therapy is not to remain on this treatment indefinitely, but to use the formula for nutrition while re-introducing foods to identify

triggers of EoE. However, as all foods have been eliminated, the trigger identification process is prolonged and requires multiple repeat endoscopies, which is a large burden on patients and might be impractical. However, the excellent effect of this treatment in both children and adults makes this an option to consider for severe EoE when patients are non-responsive to other treatments.

Systemic steroids

Corticosteroids, such as prednisone or methylprednisolone, which work systemically, are effective for the treatment of EoE[52,109]. However, these agents are not ideal for routine use for several reasons. First, owing to the multiple adverse effects that are known to occur with long-term administration (weight gain, osteoporosis, diabetes mellitus, cataracts, adrenal insufficiency and complications from immunosuppression), this class of medication can only be used on a short-term basis. If required, these agents are best used as a bridge to a different treatment option, as EoE will recur rapidly once treatment with prednisone is stopped[109]. Second, in the sole comparative RCT of prednisone compared with swallowed fluticasone, response rates were similar, but more adverse effects were noted more frequently with prednisone[52]. Current guidelines suggest that the use of prednisone should be restricted to patients who have very severe symptoms; for example, malnutrition in children, for which a rapid treatment response is required[20,21].

Leukotriene antagonists

As EoE is an allergic disease, the use of leukotriene antagonists might be appealing, as they are effective in other atopic conditions. Montelukast has been studied for the treatment of EoE, but the results are conflicting. In the initial case series reported, six of eight adults had a clinical response with montelukast at doses of 20–40 mg per day[110]. However, a subsequent study of eight children who used lower doses (4–10 mg per day) showed only a 38% response rate[111], and a study of 11 adults who took 10 mg per day reported no responders[112]. In 2016, early reports from an RCT compared maintenance therapy (rather than first-line therapy) with montelukast (at 20 mg per day) versus placebo in patients who were topical steroid responders and reported no difference in rates of symptom recurrence between the two groups[113]. These data suggest that although montelukast might be effective in some patients, its overall clinical utility is probably limited. However, this medication has a favourable adverse effect profile and can be evaluated in patients who are refractory to initial steroid or dietary elimination treatments.

Mast cell stabilizers

As mast cells have a prominent role in the pathogenesis of EoE, are present at increased densities in the oesophageal epithelium of patients with EoE, and are involved in oesophageal fibrosis and dysmotility, targeting them for the treatment of EoE is a potentially appealing option[80,114–119]. Unfortunately, the available mast cell stabilizers, such as cromoglicic acid (also known as cromolyn sodium), have not been efficacious in EoE and are currently not recommended for use[75]. It is not known whether this lack of efficacy is due to the dose, the mechanism of action or the formulation, or whether they are targeting the mast cell populations too late during the pathogenesis of EoE.

Immunomodulators

As EoE is an immune-mediated disease, immunomodulatory drugs that might decrease the immune response, such as azathioprine and 6-mercaptopurine, could be effective treatment options[22,120]. However, these medications have been studied in only one case series of three patients with EoE who were refractory to steroids[120]. In this study, patients initially responded to these medications and then relapsed with recurrent eosinophilia when treatment was stopped. Owing to the limited amount of data and the potential adverse effects, these medications are not recommended for routine use for the treatment of EoE[20]. However, in selected patients with severe EoE symptoms who are refractory to other treatment options, they could be considered.

Emerging medications

In addition to the agents discussed previously, there are several emerging medications that have either been used to treat EoE or are under study for the treatment of EoE. These include biologic agents (typically antibodies that target inflammatory factors in EoE pathogenesis) or novel small molecules that target specific pathways in EoE. Many are novel treatment targets that are based on our expanding knowledge of EoE pathophysiology. A query on clinicaltrials.gov for the term ‘eosinophilic esophagitis’ in 2016 showed 104 EoE studies listed, 38 of which were actively recruiting and 20 of which were investigating new treatments.

Biologic agents.—Several biologic medications have been evaluated for EoE. In a pilot study of three patients with steroid-refractory EoE, the TNF inhibitor infliximab (5 mg/kg) was administered and no consistent treatment response was noted[121]. In addition, an RCT of the IgE-specific antibody omalizumab versus placebo in adults with EoE reported no change in eosinophil count and no difference in symptom improvement between the groups[122]. Owing to these results, neither of these agents has a current role for the treatment of refractory EoE.

The best-studied biologic agents for EoE are in the anti-interleukin 5 (anti-IL-5) class. The type 2 T helper (T_H2) cytokine IL-5 is key in the pathogenesis of EoE owing to its involvement in eosinophil maturation and activation[123]. Three RCTs have evaluated these agents in EoE, two of which tested mepolizumab (one in adults and one in children)[124,125], and one paediatric study tested reslizumab[126]. The latter remains the largest published RCT in EoE to date, with 226 children enrolled. The results of these trials were consistent, with modest to substantial decreases in eosinophil counts compared with placebo. However, these medications did not eliminate eosinophilic inflammation and few patients achieved a very low eosinophil count. Moreover, in the two paediatric studies, symptoms improved similarly in the active and placebo treatment arms, but it is important to note that the symptom measures used were not validated. Although these drugs are not currently being investigated for the treatment of EoE, both were recently approved by the FDA for the treatment of eosinophilic asthma. For patients who have severe eosinophilic asthma, which is a relatively uncommon asthma sub-phenotype, and coexisting refractory EoE, it would be possible to collaborate with a pulmonologist or allergist to treat the asthma and observe whether there is

a concomitant improvement in the EoE symptoms and histology. However, the use of these medications specifically for the treatment of EoE is off-label.

IL-13-specific antibodies have also been evaluated. As with IL-5, IL-13 is also a key T_H2 cytokine, the levels of which are increased in EoE, and it is involved in altering oesophageal gene expression and in stimulating the production of eotaxin-3, a potent chemokine that recruits eosinophils to the oesophageal epithelium[123,127]. QAX576, an IL-13-targeted antibody, was tested in a small pilot study that included 15 patients with EoE who received active medication and eight who received placebo[128]. This study showed a decrease in eosinophil counts following QAX576 treatment compared with placebo, as well as normalization of eosinophil gene expression. A similar IL-13-targeted antibody, RPC4046, was tested in a phase II RCT comprising 90 patients with EoE[129]. Preliminary data from this trial showed a significant (P <0.05) decrease in eosinophil counts and endoscopic severity, as well as a strong trend toward decreased symptoms of dysphagia, following RPC4046 treatment compared with placebo.

The IL-4-specific antibody dupilumab is currently being evaluated in a phase II study[130]. IL-4 is another T_H2 cytokine that is involved in the pathogenesis of EoE, and dupilumab was shown to have efficacy for both asthma and atopic dermatitis[131,132]. However, no results are yet available for EoE.

Small molecules.—In addition to the biologic agents, there are also small molecules that are being studied. OC000459 is an antagonist of prostaglandin D2 receptor 2 (PTGDR2), which is present on T_H2 cells and eosinophils, and therefore blocks the binding of prostaglandin D2 (REF. 133). In a pilot RCT of OC000459 in 26 adults with EoE, there was a modest but substantial decrease in eosinophil count and the treatment was well tolerated[133]. This class of medication remains under current clinical evaluation for the treatment of EoE. Losartan, an angiotensin II receptor antagonist, is also under early clinical investigation in EoE for its antagonistic effect on TGFβ, which is a major profibrotic factor in EoE[115]. Results using this agent in EoE are not yet available.

In the context of the controversy about the use of PPIs for EoE as noted earlier, a correspondence reported a response to vonoprazan, a novel potassium-competitive acid blocker, in four patients with EoE who had previously not responded to treatment with PPIs[134]. Although this report adds to the controversy that surrounds the overlap between EoE and GERD, given that a non-PPI medication for the treatment of GERD seems to be effective for EoE, it also highlights that some patients who have EoE that is difficult to treat might have overlapping GERD[135]. In these patients, the treatment of GERD should be maximized if there is a symptomatic response or if the PPI therapy results in some improvement in oesophageal eosinophil counts. Data have shown that patients who rapidly metabolize PPIs (owing to a specific cytochrome P450 2C19 (CYP2C19) genotype) might lose an initial response to PPI treatment if the dose is lowered[136], and this issue could also be considered as a cause of poor responses in some patients.

Oesophageal dilation

The discussion thus far has centred on pharmacological and dietary treatments. However, there are patients who will not respond (or might not tolerate) any of the available options. For these patients, if they have evidence of fibrostenotic changes on endoscopy and symptoms of dysphagia, they could benefit from an oesophageal dilation programme to open oesophageal strictures and improve the calibre of the oesophagus. Importantly, endoscopic assessment of oesophageal calibre has fairly poor sensitivity, but reasonable options include assessing calibre with a barium esophagram, objectively measuring oesophageal calibre endoscopically with the so-called ‘balloon pull-through’ technique, or carrying out empirical dilation to assess for mucosal signs of dilation (rents or ‘dilation effect’)[137–141]. Although there were initial questions in regard to the safety of oesophageal dilation in EoE[142,143], experience accumulated from multiple centres has now established it as a safe procedure, with a perforation risk of 0.3%, which is similar to the risk of oesophageal dilation for other causes of strictures[140,144–149]. Although dilation of the oesophagus does not affect the underlying inflammatory process[146] and ongoing inflammation can lead to recurrent stricturing and the need for repeat dilation, this method is an effective way to improve symptoms and decrease the risk of food impaction in patients with fibrostenosis[150]. As previously described, this approach is also a good option for patients who have a histological response to anti-inflammatory treatment but have ongoing dysphagia symptoms due to a persistent oesophageal stricture.

Conclusions

Refractory EoE is a challenging condition to manage for many reasons. Although the condition is conceptually easy to describe, it is difficult to operationalize and define. Data to guide evidence-based decision-making are limited, and treatments that are currently available have suboptimal efficacies. Refractory EoE is also commonly encountered, which directly highlights the lack of medications that are targeted to the oesophagus and the difficulty of being able to reliably detect food triggers of EoE.

For the purposes of this Review, refractory EoE has been defined as persistent eosinophilia (≥15 eos/hpf) in the setting of incomplete resolution of the primary presenting symptoms and incomplete resolution of endoscopic findings following a PPI trial and after treatment with either topical steroids or dietary elimination. In this situation, it is important to assess the multiple possible causes for a lack of response, as well as treatment complications and an incorrect diagnosis of EoE. If non-response is confirmed, the approach is to first maximize the initial treatment, and then to switch from topical steroids to dietary elimination, or vice versa. If there is still no response, alternative treatments could be considered in selected patients, including custom topical steroid formulations, elemental formula, a short course of prednisone, immunomodulators or montelukast. Although there are no clinical data in regard to combination therapy, this modality could be considered as well. Patients with refractory EoE are also ideal candidates for clinical trials, as there are several promising agents that are under various phases of preclinical and clinical development, including biologic agents that target the mechanisms of EoE pathogenesis. If the safety and efficacy profiles of these novel agents are found to be acceptable, it is

conceivable that biological agents will find a niche in the treatment of refractory EoE. There is also hope that oesophageal-specific formulations of topical steroids will decrease non-response rates in EoE. For patients with refractory EoE who have oesophageal strictures or narrowing and symptoms of dysphagia, an oesophageal dilation programme is effective for improving symptoms.

Despite the difficulties with the current management strategy for patients with refractory EoE, it is an exciting time for therapeutic development in EoE and the future is bright. Given our increasing knowledge of the pathogenesis of EoE, as well as the experimental agents that are already under development, there are important opportunities to improve patient care and treatment algorithms. Both patients and healthcare providers should be optimistic for new approaches for the treatment of refractory EoE in the future.

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Key points

- Refractory eosinophilic oesophagitis (EoE) can be defined as persistent eosinophilia with incomplete symptom resolution, and persistent endoscopic findings after a PPI trial and after topical steroid treatment or dietary elimination
- Depending on the treatment modality, non-response to topical steroid or dietary elimination in EoE can be in the range of 20–50%
- Following non-response, it is important to systematically assess for explanations (for example, non-adherence; incorrect dosing, formulation or administration; ongoing allergen or food trigger exposure; inadequate dietary elimination; and validity of original diagnosis)
- Few clinical predictors of non-response have been identified to date
- Topical steroid or dietary elimination treatments should be maximized before switching between treatment modalities
- Second-line treatment options include systemic corticosteroids, elemental formula, leukotriene antagonists, immunomodulators and experimental agents in clinical trials

Box 1 |

Proposed definition of refractory EoE

After a PPI trial, and following treatment with either topical corticosteroids or dietary elimination, refractory EoE can be defined as:

- Persistent oesophageal eosinophilia (≥15 eos/hpf)
- Incomplete resolution of the primary presenting symptoms
- Incomplete resolution of endoscopic findings of EoE

EoE, eosinophilic oesophagitis; eos/hpf, eosinophils per high-power field.

Box 2 |

Potential explanations for non-response

For topical corticosteroids:

- Non-adherence
- Dose too low
- Inappropriate administration
- Suboptimal formulation (low dwell time)
- Persistent allergen exposure
- Superimposed infection (for example, with *Candida* spp. or herpes simplex virus)
- Stricture causing persistent symptoms
- Incorrect diagnosis of EoE

For dietary elimination:

- Non-adherence
- Inadvertent contamination
- Correct trigger, or triggers, not eliminated and/or persistent allergen exposure
- Stricture causing persistent symptoms
- Incorrect diagnosis of EoE

EoE, eosinophilic oesophagitis.

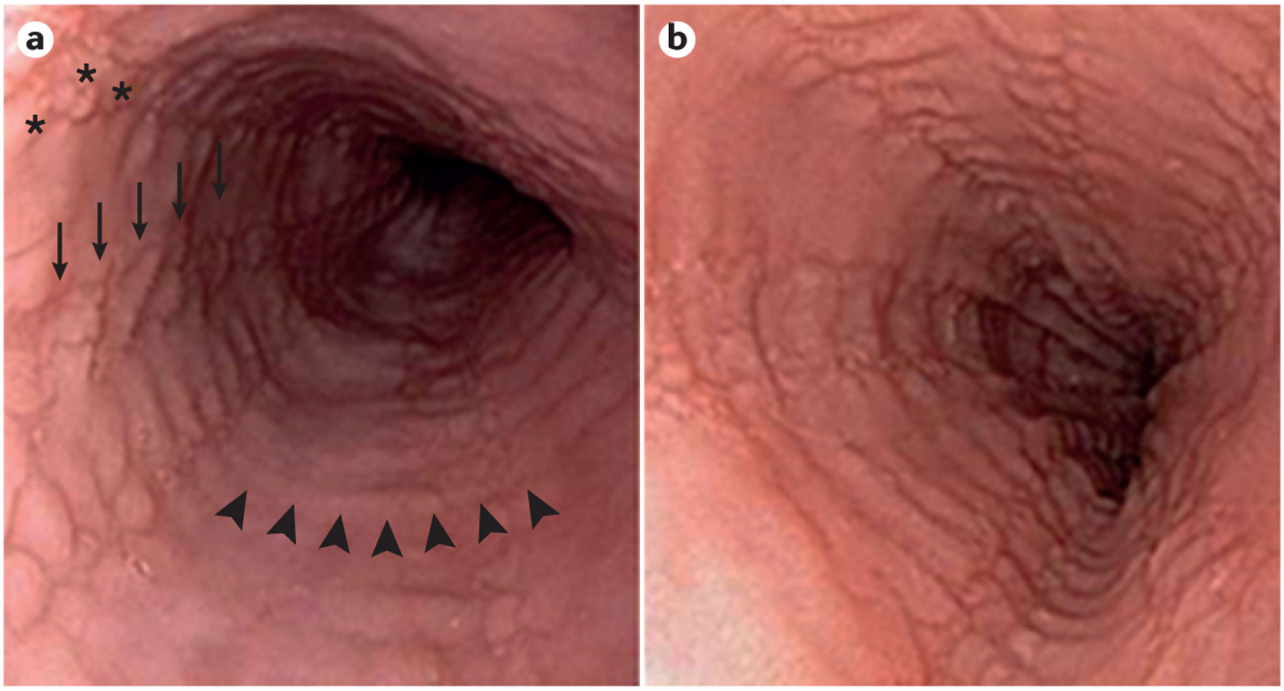

Figure 1 |. Endoscopic appearance of refractory EoE.

Paired endoscopic images of the oesophagus of a patient with eosinophilic oesophagitis (EoE) at diagnosis (part **a**) and after treatment with oral viscous budesonide at a dose of 1 mg twice daily (part **b**). At both time points, the patient remained symptomatic with dysphagia and there is no change in either the endoscopic findings (oedema (a diffuse loss of vascular markings), rings (arrowheads), subtle exudates (asterisks) and furrows (arrows) are seen at both time points) or histological findings (60 eos/hpf at diagnosis and 55 eos/hpf post-treatment). Eos/hpf, eosinophils per high-power field.

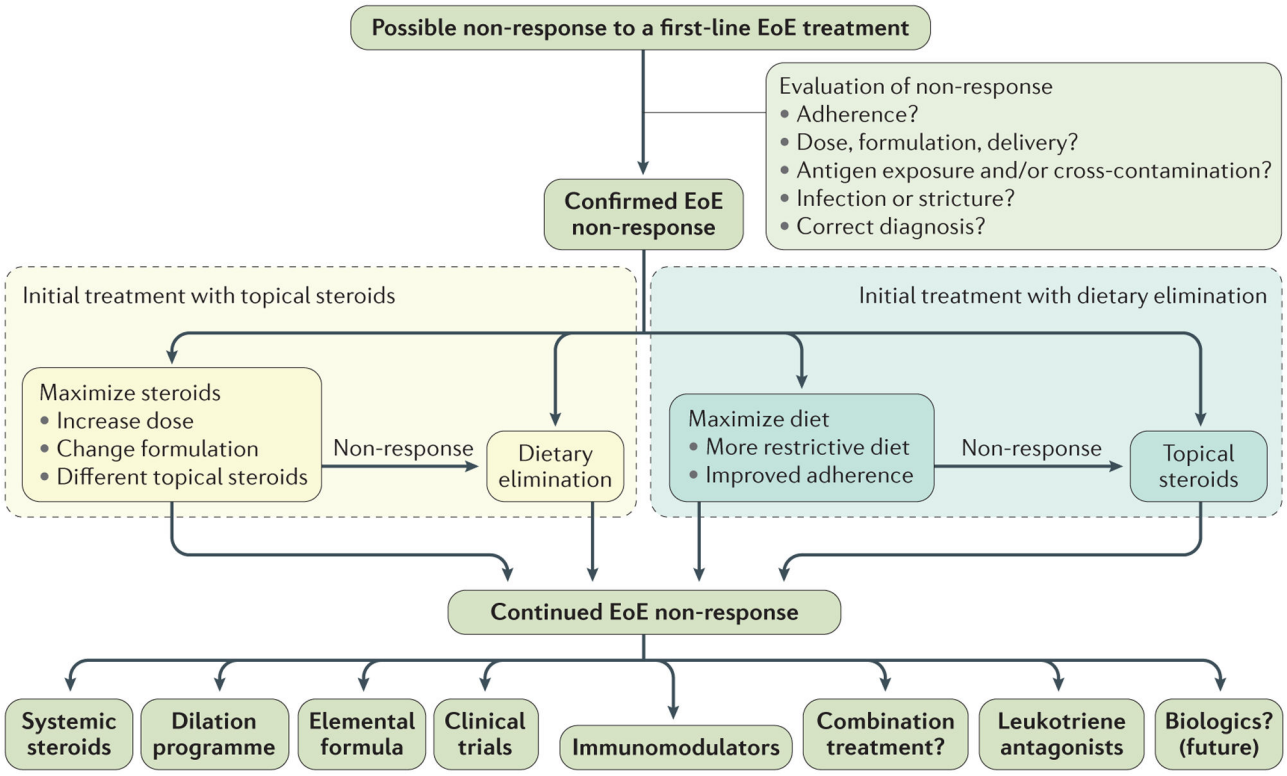

Figure 2 |. Clinical approach to refractory EoE.

A suggested treatment algorithm for patients with eosinophilic oesophagitis (EoE) after a PPI trial who do not respond to a either topical steroid or dietary elimination treatment. When a patient might have non-response, the first step is to evaluate the potential causes of non-response and correct them. If non-response is confirmed, the next step will depend on the initial treatment strategy. If the original treatment was with topical steroids, then this modality could be optimized or the patient could be switched to dietary elimination. If the original treatment was dietary elimination, this could be maximized or the patient could be treated with topical steroids. If there is continued non-response, there are a wide range of options the choice of which will depend on the patient and disease characteristics. Often these patients are suitable candidates for participation in clinical trials of emerging treatment agents.

Table 1 |

Frequency of non-response in RCTs of topical corticosteroids, by histological, symptom and endoscopic outcome measures

Author, year	Medication and dose	Patient group	Most stringent histological response threshold reported	Non-response for most stringent level (%)	Non-response for <15 eos/hpf level (%)	Symptom response	Endoscopic response
Konikoff, 2006 (REF. 51)	• Fluticasone • 880 μg per day	Children	≤1 eos/hpf	50	45*	Decreased vomiting	Decreased furrows distally
Schafer, 2008 (REF. 52)	• Fluticasone • 880–1,760 μg per day	Children	<1 eos/hpf	44*	22*	Presenting symptom improved	–
Dohil, 2010 (REF. 53)	• OVB • 1–2 mg per day	Children	≤6 eos/hpf	13	23*	Improvement in Symptom Scoring Tool	Improvement in Endoscopy Scoring Tool
Straumann, 2010 (REF. 54)	• OVB • 2 mg per day	Adults	<5 eos/hpf	28	11‡	Improvement in the SDI	Improvement in exudates and furrows, not rings
Peterson, 2010 (REF. 62)§	• Fluticasone • 880 μg per day	Adults	≤5 eos/hpf	85	69	No difference versus comparator arm with a 7-point dysphagia scale	–
Alexander, 2012 (REF. 56)	• Fluticasone • 1,760 μg per day	Adults	>90% decrease in eosinophil counts	48	–	No difference versus comparator using the MDQ	30% with resolution of pre-treatment findings
Dellon, 2012 (REF. 55)	• OVB • 2 mg per day	Adults	<1 eos/hpf	36	27	No difference versus comparator using the MDQ	Improvement in endoscopic findings except stricture
Moawad, 2013 (REF. 61)§	• Fluticasone • 880 μg per day	Adults	<7 eos/hpf	81	-	No difference in fluticasone arm using the MDQ	Decreased exudates
Butz, 2014 (REF. 57)	• Fluticasone • 1,760 μg per day	Adolescents and adults	≤1 eos/hpf	35	23	Decreased heartburn	–
Gupta, 2015 (REF. 58)	• OBS • 2.8–4 mg per day	Children	≤1 eos/hpf	23	–	No difference versus comparator using the Clinical Symptom Score	–

Author, year	Medication and dose	Patient group	Most stringent histological response threshold reported	Non-response for most stringent level (%)	Non-response for <15 eos/hpf level (%)	Symptom response	Endoscopic response
Miehlke, 2015 (REF. 59)	• BET and BVS • 2–4 mg per day	Adults	<16 eos/mm^2	6	–	No difference versus comparator using the SDI	Decrease in Endoscopic Severity Score versus comparator
Dellon, 2017 (REF. 60)	• OBS • 4 mg per day	Adolescents and adults	≤1 eos/hpf	69	53	Improvement in the Dysphagia Symptom Questionnaire	Improvement in the EREFS score

BET, budesonide effervescent tablet; BVS, budesonide viscous solution; EoE, eosinophilic oesophagitis; eos/hpf, eosinophils per high-power field; EREFS, EoE endoscopic reference score; MDQ, Mayo Dysphagia Questionnaire; OBS, oral budesonide suspension; OVB, oral viscous budesonide; RCTs, randomized controlled trials; SDI, Strumann Dysphagia Instrument.

*Calculated from individual patient data presented in the manuscript.

‡For the reported threshold of <20 eos/hpf rather than <15 eos/hpf.

§Patients in these studies had EoE, but not EoE as defined by consensus guidelines.