Evidence-based treatments for eosinophilic esophagitis: insights for the clinician

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***Abstract*:** Eosinophilic esophagitis (EoE) is a chronic inflammatory disorder characterized by symptoms of esophageal dysfunction and eosinophil-predominant inflammation. Left untreated, EoE progresses to fibrous remodeling and stricture formation that impairs quality of life. Therefore, EoE requires either repeated treatments or maintenance therapy. Current guidelines recommend swallowed topical corticosteroids (STCs), proton-pump inhibitors (PPIs), or dietary intervention as initial options to induce and maintain long-term disease remission. Impractical exclusive elemental diets and suboptimal allergy testing-directed food avoidance paved the way for empirical elimination diets. These are moderately effective and highly reproducible in inducing EoE remission and allow for identification of specific food triggers. Step-up strategies, including two- and four-food rather than six-food elimination diets, should be considered as initial approaches for dietary treatment in patients of all ages, as they reduce the need for endoscopic procedures, shorten diagnostic processing time, and avoid unnecessary restrictions. Formulations of STC originally designed for asthma therapy are suboptimal for EoE treatment, with new effervescent orodispersible tablets and viscose formulations designed to coat the esophageal mucosa providing increased effectiveness at reduced doses. The anti-inflammatory effects of PPI in EoE are independent from gastric acid secretion inhibition; despite evidence from observational research, PPIs are the most commonly prescribed first-line therapy for EoE due to their accessibility, low cost, and safety profile. Double doses of PPI only induce remission in half of EoE patients, irrespective of the drug used or patients' age. Inflammatory rather than stricturing EoE phenotype and treatment duration up to 12 weeks increase chances of achieving EoE remission. Most responders effectively maintain long-term remission with standard PPI doses. Finally, endoscopic dilation should be considered in patients with reduced esophageal caliber or persistent dysphagia despite histological remission. This article provides a state-of-the-art review and updated discussion of current therapies and newly developed options for EoE.

Keywords: budesonide, diet therapy, dilation, eosinophilic esophagitis, fluticasone, food elimination diet, food hypersensitivity, formulated food, proton-pump inhibitor, swallowed corticosteroids

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Introduction

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated inflammatory disease that is characterized by esophageal dysfunction and transmural infiltration of the esophagus by eosinophils.[1,2] EoE is diagnosed in children and adults into their 50s after demonstrating an eosinophil-rich inflammation in esophageal biopsies, taken during an upper gastrointestinal endoscopic examination carried out to study the origin of symptoms of esophageal dysfunction. In younger children and infants, these symptoms mainly consist of reflux-like symptoms, vomiting, abdominal pain, food refusal, and failure to thrive.[3] Older children and adults with EoE most commonly report solid food dysphagia, food impaction, and

non-swallowing associated chest pain.[4] Left untreated, symptoms and esophageal inflammation in EoE tend to persist over time[5,6] and patients can develop esophageal rings, focal strictures, or a long narrowing in the esophageal caliber, risk being directly related to patients' age and diagnostic delay.[7–9] Therefore, the natural course of EoE has been described as consisting of a long-lasting, probably lifelong, chronic inflammation that may progress into fibrous remodeling of the esophageal wall, with collagen deposition, lamina propria fibrosis, and esophageal rigid strictures, as the disease evolves from childhood into adulthood. Esophageal remodeling may result in several disease-inherent and procedure-related complications,[10] although not in all patients.[7] Because of its chronicity, symptoms of EoE usually persist over time, or intensify as the fibrotic complications of the disease develop, with the episodes of food impactions, that occasionally require urgent medical attention, being more common.[11] Patients frequently develop adaptive behaviors to cope with the symptoms, such as becoming slow and careful eaters, drinking water with every meal, and avoiding dining out and other situations where there is risk of food impaction and associated anxiety.[12] A considerable proportion of adult EoE patients suffer from mental distress[13] or psychiatric comorbidity,[14] and become hypervigilant around food.[15] Social relationships, which generally revolve around food, diminish, potentially leading to social isolation and withdrawal. Although not associated with mortality or risk of malignancy, acute complications of EoE include mucosal tears produced spontaneously while trying to dislodge impacted food or following endoscopic procedures, and may be complicated by esophageal perforation, which sometimes constitutes the initial presentation of EoE.[16–18] As a result, a significant morbidity may be associated with EoE, negatively impacting on the health-related quality of life (HRQoL) of patients[19,20] and clearly indicating a need to treat patients with active disease or persistent symptoms.

EoE is a young disease, the first cases being described in the 1970s and 1980s as a particular form of eosinophilic gastroenteritis with esophageal involvement.[21–26] These early cases established the frequent association of EoE with atopy, subsequently defined as a landmark of the disease, that involves a Th2 immune reaction to food and/or aeroallergens in its pathophysiology:[27] Most patients with EoE also present with a personal and/or family history of several atopic manifestations,[28] which are well recognized as a factor in the appearance of the disease.[29]

The first characterization of EoE as a distinctive clinico-pathological syndrome, different from eosinophilic gastroenteritis, was proposed less than three decades ago[30,31] and the number of cases reported across all continents has sharply expanded since then, with most cases being diagnosed in Europe and North America. Currently, EoE represents the most common cause of chronic or recurrent esophageal symptoms after gastroesophageal reflux disease (GERD). It is the leading cause of dysphagia in children and young adults in developed countries, with, according to several studies, a prevalence that exceeds 100 cases per 100,000 inhabitants.[32,33] As a result, EoE now represents a chronic common health problem in gastroenterology and allergy clinics, and a significant burden on health care systems, in which a well-recognized diagnostic delay, the need for endoscopy with biopsies to diagnose the disease and monitor the response to treatments, and the costs of therapies are estimated to be $2300 per year in the United States.[34] This increases considerably, up to $4001 per year, in pediatric patients, far exceeding the cost of care of Crohn's and celiac diseases.[35]

The expanding epidemiology of EoE has allowed the development of multiple trials and meta-analyses to identify effective therapies. These include dietary interventions to target the allergic nature of EoE, several drugs with anti-inflammatory effectiveness, and endoscopic dilation to provide symptom relief in patients with esophageal strictures or narrow caliber esophagi and persistent dysphagia/food impaction, despite effective anti-inflammatory treatment. Intense research efforts are being undertaken to provide treatment options to the proportion of patients who are still unable to have their disease controlled with current therapeutic options.[36,37] Several consensus documents and clinical practice guidelines released during the last decade[1,38–41] have provided a structured and evidence-based framework for treating patients with EoE, trying to maximize the results of available therapies. However, substantial variations in adherence to guidelines regarding treatment choice and assessment of response have been documented,[42–46] which has limited assessment of the effectiveness of the different interventions available for EoE.

This article aims to provide an updated overview on the different alternatives to effective treatment of patients with EoE from an evidence-based approach. The effectiveness, advantages, and limitations of dietary, pharmacological, and endoscopic options will be reviewed and advice for their implementation in clinical practice will be provided.

Dietary therapy: the different approaches to target the primary cause of EoE

Elemental diets and the definition of EoE as a food allergy

EoE was identified as a particular form of food allergy shortly after its recognition as a distinct disorder in a seminal research: a group of children with esophageal symptoms and eosinophilia attributed to GERD and refractory to antisecretive drugs, and even fundoplication, were exclusively fed with an elemental formula, based on amino acids and lacking all antigenic capacity, for a minimum of 6 weeks.[47] Symptoms and esophageal eosinophilia improved in all the 12 patients who adhered to the diet. Esophageal eosinophilia reduced dramatically from baseline in the 10 patients who also underwent upper endoscopy, with 90% of them achieving histological remission of EoE. This research first demonstrated food allergy as the underlying cause of EoE and provided evidence on the effectiveness of a dietary intervention to treat these patients. Subsequent studies confirmed this observation. A meta-analysis of all 12 studies available on elemental diet in 2014 provided, in terms of achieving histological remission, a very high combined effectiveness for this intervention of around 91%.[48] All were observational studies mostly carried out in pediatric patients. Recent research carried out in adults has obtained similar results.[49,50]

Despite being one of the most effective therapies for EoE, able to achieve rapid histological remission, at times within 2 weeks,[49] the multiple drawbacks of avoiding all types of food other than an artificial formula quickly proved limited in clinical practice. Being unappealing led to poor compliance, with some adult patients abandoning the diet on the first day,[49] and many small children requiring nasogastric tube delivery to ensure a proper intake of calories.[51] Exclusive elemental diet feeding also carries significant psychological and social difficulties, as well as diminished HRQoL.[19] An additional barrier for its implementation is the high cost of elemental formulas not being universally reimbursed by insurance companies. Finally, long-term avoidance of solid food in children under 2 years old or with known feeding dysfunction may lead to delayed oral-motor skill development.[52] Even when successful in inducing remission, the dietary reintroduction process after elemental diet therapy is lengthy, and requires multiple endoscopies with biopsies and several months of continued nutritional support while normal diet is gradually returned.[53] All this significantly reduces the real possibility of using exclusive elemental diets in clinical practice as a bridge therapy for highly refractory infants and toddlers while waiting for investigational drugs, as well as for patients who wish to remain in remission while investigating the casual role of unusual foods and aeroallergens in their disease. Flavored formulas are recommended as too is the combining of elemental formula with solid foods which have the least probability of being involved as food triggers.[54] All these aspects and utilities, however, have not been adequately investigated as yet.[55]

Allergy testing-directed food elimination: the second chapter in the dietary therapy for EoE

The multiple difficulties of implementing elemental diets for EoE as a feasible option for most patients soon led to the search for new alternatives. Avoiding all foods that tested positive, using such tests as the skin prick test, prick-prick test, atopic patch testing, or food-specific serum IgE, was the next dietary approach. After some initial reports biased by the inclusion of patients managed with elemental diets,[56] a meta-analysis that combined the results of all studies using the above approach provided a summary estimate for effectiveness in achieving remission of less than 50%.[48] This was even lower in the studies carried out in adults compared with children (32.2% *versus* 47.9%, respectively). A wide heterogeneity was also demonstrated between the different studies, indicating unlikely reproducibility of individual research results. Despite the variety of methods to assess allergic reaction to food used in the studies, no particular one proved superior. The main criticism is that food triggers were not identified by histological recurrence after challenging patients who were in clinico-histological remission, but rather by immediate symptom relapse reported by parents after individual food reintroduction. EoE

is characterized by a low correlation between symptoms and histological activity,[57] even when disease-specific validated instruments are used.[58,59] Given this, the finding of very low accuracy of skin allergy testing to detect milk, wheat, and egg (the most common foods involved in triggering EoE, as proved by empirical elimination diets),[56,60,61] was expected and insufficient to guide clinical practice. Combining results from several allergy tests did not produce better results.[61] The low reproducibility of some initial studies leads to the European Academy of Allergy, Asthma and Immunology to state that an IgE-mediated food allergy was not involved in EoE, and the elimination diets based exclusively on IgE sensitization results were not able to improve EoE in a significant number of patients.[62] The use of non-IgE-based allergy tests, such as atopic patch testing, did not provide significant clinical benefit either.[63,64]

The evolving approach to empiric elimination diets

The empirical dietary approach in EoE consists of eliminating from patients' diets those foods more commonly associated with food allergy, irrespective of allergy testing results. This subsequent strategy was first assessed by Kagalwalla and colleagues in 2006.[65] They simultaneously removed from patients' diets the six most common food antigens related to allergy – milk, wheat, egg, soy, nuts, and fish and seafood – for a period of 6 weeks. Three out of four patients achieved histological remission similar results to those achieved with elemental diets, indicating that at least one of the eliminated foods was a trigger for the disease. Identifying specific triggers was made by sequential food reintroduction and endoscopy with biopsy after each reintroduction.[66] Subsequent studies that followed this strategy demonstrated that the so-called six-food elimination diet (6-FED) provided the most homogeneous results for patients of all ages, with 70% of them being able to achieve histological remission of EoE after food avoidance.[48]

It must be pointed out the 6-FED is only a means of achieving normalization of the mucosa, as a benchmark from which to identify the food or foods that trigger and maintain the disease in each individual patient. Therefore, patients who achieve remission after any dietary approach should proceed to a sequence of reintroduction of individual foods, with repeated endoscopies and biopsies, which will allow a clear identification of the food cause for EoE in each particular case. This food challenge will ensure that only the food or foods that cause EoE are avoided while the non-offending foods are permitted, thus facilitating long-term adherence to diet therapy.

The 6-FED can now be considered an obsolete approach, despite being the most commonly used empirical elimination diet to treat EoE in the past. However, it has been essential in discovering the frequency with which each food triggers EoE. Several studies have led to identifying milk as the main trigger, followed by cereals with gluten, eggs, and soy or legumes, respectively, while the role of nuts, and fish and seafood is minimal.[65,67–69] Therefore, the next dietary approach consisted of a four-food elimination diet (4-FED), in which milk, wheat or gluten-containing cereals, eggs, and legumes or soy were temporally removed from patients' diets. The first multicenter prospective trial on this diet, carried out in Spain in adult patients, provided evidence that one single food was involved in EoE in half of the patients, with the remaining having two independent food triggers for their disease.[70] A 4-FED was assessed later in children in the United States, which demonstrated again that milk was the major food involved in EoE, followed by gluten. Overall, this approach provided 54–64% effectiveness in terms of inducing clinico-histological remission of EoE.

The next notable stage consisted of initially restricting milk and gluten-containing cereals, while eggs and legumes remained, thus giving rise to the two-food elimination diet (2-FED). This approach was assessed in a multicenter study involving 130 adult and pediatric patients, using a step-up approach to dietary treatment. Forty-three percent of EoE patients treated with a 2-FED achieved symptomatic and histological remission; non-responders were offered a 4-FED, which provided an overall combined efficacy of 60%. A 6-FED was reserved as a final rescue therapy for non-responders to the previous diets and provided an overall efficacy of 80%. Notably, no differences were observed in terms of efficacy between children and adults.[71]

A step-up empiric elimination diet demonstrated reducing by 20% the number of endoscopic exams and the length of time on a restrictive diet, regarding starting with a 6-FED. Also it allowed

to early identify those patients with only one or two offending foods, who were the best candidates for long-term maintenance with dietary therapy: 90% of patients who exclusively responded to the last rescue 6-FED had at least three independent food triggers for EoE, making it very difficult to follow this restrictive diet in the long term. In fact, escalating to a 6-FED was ruled out as a good option for most patients who did not respond to a 4-FED.[72]

The next obvious stage in empirical diet therapy for EoE was a single food elimination diet, namely, a milk-free diet. Most research on this approach overestimated the true effectiveness of this intervention either due to the biased inclusion of patients with a previous IgE-mediated reaction to milk, who overcame it either spontaneously or after oral immunotherapy,[73] or by the recruitment of patients concomitantly treated with proton-pump inhibitors (PPIs),[74,75] a drug that produces anti-inflammatory effects in half of the patients with EoE.[76] The most accurate figures for the efficacy of a milk-free diet in EoE are probably around 44%, as recently demonstrated by a randomized controlled trial (RCT) exclusively reported as an abstract,[77] with further studies being required to confirm these results.

The efficacy of long-term dietary therapy for EoE remains largely unknown, since it has only been partially assessed in a small number of short patients' series.[66,68,69,78,79] In addition, according to the studies carried out in the United States[78,79] and Australia,[69] the results have been quite disappointing due to only 50% of patients adhering to the diet beyond 1 to 2 years after finalizing the food reintroduction protocol; this proportion reached 88% in research carried out in Spain.[68] As dietary therapy maintained effectiveness in adherent patients, it is important to identify the complex factors that influence adherence to long-term maintenance of elimination diets in order to select the best candidates. Barriers include patient's perception of diet effectiveness, the limitation it imposes on social situations and anxiety related to the diet.[79]

As previously mentioned, patients with EoE experience impaired HRQoL, not only as a result of their symptoms but also in relation to the social and emotional impact of their disease, such as eating in public and anxiety around choking.[80] The potential effects of dietary therapy on further impairing HRQoL with EoE are controversial, and while critics of this treatment modality highlight the negative effect of food avoidance, there is some evidence that points to the contrary. Adult patients treated with a 6-FED diet reported HRQoL improvements, evaluated with the generic instrument Sort Form (SF)–36,[67] and although a prospective study of adult Spanish patients with EoE, evaluated with the disease-specific EoE Quality of Life Adult (EoE-QoL-A) questionnaire, found emotional impact was significantly worse in those undergoing dietary restriction, the overall scores were not significantly worse than those without restriction and undergoing pharmacologic therapies.[12] As for children, HRQoL was reported to decrease after dietary therapy,[81] as measured with the Patient Asessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QoL) questionnaire. However, this is an instrument validated in patients with dyspepsia, GERD, or gastroparesis,[82] and not in EoE. The use of a disease-specific validated instrument such as the Pediatric Quality of Life Inventory (PedsQL)-EoE module found lower HRQoL scores among children treated with diets,[83] but increased after effective diet-induced disease remission.[75]

Maximizing the benefits of dietary therapy for EoE in the short and long term will require, apart from choosing the appropriate dietary approach, a careful selection of appropriate candidates, paying attention to patent age, lifestyle and life stage, motivation and willingness to undergo repeated endoscopies, and financial and educational resources.[80] Dietary therapy should be patient-centered and all treatment alternatives must be discussed with the patients and/or the family before making a decision. The most appropriate dietary approach should then be selected and patient support provided to guarantee appropriate nutrient intake and ensure avoidance of cross-contamination. In order to overcome long-term treatment restrictions and minimal impact on HRQoL, patients should receive support and, preferably written, information before and during the study process, as well as advice on coping with avoidance of common food stuffs and resources to replace eliminated foods.[55,84]

Topic corticosteroid therapy: keys to target the esophageal mucosa

Shortly after the description of EoE, corticosteroids with reduced bioavailability (beclomethasone

and budesonide), swallowed instead of inhaled, were proved for the first time to be as effective as systemic steroids in inducing clinical and histological remission of the disease in a small series of four children.[85] Later on, fluticasone propionate also offered evidence of effectiveness in treating EoE,[86–88] and mometasone furoate was recently added to the list of drugs with potential benefit in this disorder.[89,90]

An RCT compared swallowed topical corticosteroids (STCs) with oral prednisone:[91] after 4 weeks of treatment, both options were shown to have the same effectiveness in inducing clinical and histological remission of EoE. Systemic corticosteroids presented no advantages in terms of symptom resolution, relapse rates, or time to relapse, but had significantly more severe adverse effects. Therefore, systemic steroids are generally not recommended in EoE[1] and have been replaced by topic corticosteroids to treat EoE.

With more than 1000 patients enrolled in RCTs worldwide, STC can be considered to be the best studied drug class in EoE.[92] The superiority of fluticasone propionate over placebo to induce clinical and histological remission of EoE,[93] and of any other formulation of STC, has been corroborated in numerous systematic reviews and meta-analyses that involve RCTs carried out in children and adults over the last two decades.[93–98] Despite slight differences in defining histological remission across the different studies, both budesonide and fluticasone propionate are shown to be significantly superior to placebo in reducing peak eosinophil densities below the diagnostic threshold of 15 cells/hpf (odds ratio, OR = 24.6, 95% confidence interval, CI = 7–86.8),[95] in achieving complete histological remission (<6 eosinophils/hpf; OR = 35.82, 95% CI = 14.98–85.64),[97] and in restoring a normal endoscopic appearance in EoE (OR = 3.51, 95% CI = 1.47–8.36). However, a uniform and convincing remission of symptoms could not be demonstrated in all cases, mainly because several trials used non-structured or validated instruments to assess EoE symptoms. Differences in drug effectiveness have also been demonstrated: a systematic review found budesonide as significantly superior to placebo in terms of symptomatic relief (OR = 7.20, 95% CI = 2.15–24.05) but not fluticasone propionate (OR = 1.27, 95% CI = 0.44–3.65).[96] The variable drug dosages used in the different RCTs, but specifically the different drug administration methods used to deliver STC inside the esophageal lumen, explain the reported differences in the effectiveness of fluticasone propionate and budesonide to target EoE. Fluticasone and budesonide have shown comparable potencies, but they were used in different vehicles to be deposited on the inner esophageal surface: while fluticasone has been mostly administered from multi-dose inhalers, nasal drops, or aqueous nebulizer solutions, patients should swallow the medication to coat the esophageal mucosa with it – budesonide has been mostly applied with viscous solutions and more recently with orodispersible tablets . This essential difference was clearly demonstrated in an RCT that compared two formulations of budesonide (oral viscous and nebulized) administered at the same doses for same periods, and showed that oral viscous budesonide provided a higher level of esophageal coverage due to a longer contact time between the mucosa and the medication, and this resulted in greater reduction of esophageal eosinophil counts and endoscopic normalization.[99] Effectively administering a topical treatment for EoE poses a challenge due to the anatomical and functional characteristics of the esophagus: apart from its tubular structure with a distal outlet toward the stomach, its upright position favors the effect of gravity. Peristaltic movements will quickly conduct any content deposited inside the esophagus to the gastric cavity. Food and drink also contribute to the dragging of the contents of the lumen into the stomach, and in fasting, the secretion of saliva contributes to the continuous washing of the interior of the organ.

Viscous corticosteroid solutions, especially those containing budesonide[100,101] but also fluticasone[86] and mometasone,[90] have improved STC delivery in EoE, with effervescent orodispersible tablets that use saliva to transport and adhere the drug to the esophageal inner surface being the latest innovation. A budesonide orodispersible tablet (BOT) formulation, that provided an efficacy of almost 100% in achieving histological remission after 2–6 weeks of therapy,[102,103] is already approved by the European Medicines Agency as the first drug to treat EoE in adult patients and is available in several European countries. In order to maximize the chances of achieving remission of symptoms together with normalization of the esophageal histology, the recommended duration of induction treatment with this medication is 6–12 weeks. Maintenance of clinical, histological, and endoscopic remission with the same budesonide

Table 1. Swallowed topical steroid initial dosing to treat eosinophilic esophagitis.

Drug	Target population	Induction dosing (usually divided doses)	Maintenance dosing (usually divided doses)
Fluticasone propionate[a]	Children	880–1760 µg/day	440–880 µg/day
	Adults	1760 µg/day	880–1760 µg/day
Fluticasone propionate suspension[b]	Adults	2000–4000 µg/day	Not reported
Budesonide viscous solution[c]	Children[d]	1–2 mg/day	1 mg/day
	Adults	2–4 mg/day	2 mg/day
Budesonide orodispersible tablet[e]	Adults	2 mg/day	1 mg/day
Mometasone furoate	Adults	800 µg/day[f]	Not reported
Mometasone viscous suspension[g]	Children	750–1500 µg/day, depending on patient's height	Not reported
Beclomethasone dipropionate[h]	Adults	320 µg/day	Not reported

[a]If an inhaler is used, the patient should be instructed to puff the medication into their mouth during a breath hold. Regardless of the form of administration (nebulized or swallowed nasal drops), patients should fast at least 30–60 min after medication in order to minimize esophageal drug clearance.
[b]The medication was formulated as a viscous suspension by mixing powdered fluticasone with a hydroxypropyl methylcellulose gel at a concentration of 1 mg/8 ml.
[c]Oral viscous budesonide preparation consists of mixing 1–2 mg budesonide with 5 mg of sucralose or similar.
[d]Specific doses in children will be determined by age, height, or weight.
[e]Available in several European countries, the daily dose is divided into two doses.
[f]Four doses of 50 µg applied orally by spray four times daily.
[g]A 150 mg/ml suspension is composed of powder forms of mometasone furoate, hydroxypropyl methylcellulose, potassium sorbate, citric acid, stevia, sodium benzoate, and liquid flavoring agent.
[h]Provided at inhalation aerosol 80 µg per puff; two puffs swallowed twice a day.

compound was demonstrated in the vast majority of patients who received either the same or half of the dose used to induce remission.[104] After 48 weeks of treatment, 73.5% of patients receiving BOT 0.5 mg twice daily and 75% receiving BOT 1.0 mg twice daily were in persistent remission compared with 4.4% of patients in the placebo group. Histologically confirmed candidiasis was seen in 7.4% and 2.9% of patients treated with BOT 0.5 and 1.0 mg twice daily, respectively. Finally, mean morning cortisol levels at baseline did not change at the end of treatment.

An orally disintegrating tablet formulation of fluticasone given at several doses over 8–12 weeks has proved superior to placebo in inducing clinical, endoscopic, and histological remission of EoE.[105,106] An ongoing phase III trial will also evaluate the effectiveness of this compound for an additional 40-week maintenance phase in adults with EoE (ClinicalTrials.gov Identifier NCT04281108). Dose ranges and specific instructions for administration of topical steroids in EoE are presented in Table 1.

STC appears to have a favorable safety profile when used to treat EoE, with no serious side effects in the short term (mostly limited to oropharyngeal and esophageal Candida infections). This complication has been described in up to 16% of patients of all ages irrespective of taking viscous formulas, orodispersible tablets, or aerosol metered doses,[103,106–108] who were generally asymptomatic and diagnosed incidentally in endoscopies during post-treatment evaluation. Candidiasis in EoE easy response to specific therapy, and no need to withdraw STC was found . Neither was the rate of

candidiasis increased when STCs were used in the long term.[101,104]

Recent concerns about the potential risk of suppressing systemic cortisol by topic corticosteroids have arisen, especially in children. Observational studies consisting in short series of patients with EoE[109,110–112] have provided conflicting results. This is due to employing different methods of determining adrenal function, which included measuring basal cortisol levels, low-dose adrenocorticotropic hormone (ACTH) stimulation test, or standard dose ACTH stimulation test, as well as cortisol levels after ACTH at different times after the stimulation dose.[113] In contrast, well-designed RCTs involving children[114] and adults[88,102,103] who received STC in the short and long term to treat EoE[104,115,116] reported no clinical data of adrenal suppression or growth impairment. Until more information is available, to prevent adrenal insufficiency cortisol monitoring may be advisable for children with EoE if they receive high doses of STC for long periods, or in cases of concomitant use of corticosteroids by other routes (oral, inhaled, or nasal) to treat concomitant atopies.[1] Finally, observational studies assessing the long-term use of STC detected no esophageal dysplasia or mucosal atrophy after a 5-year therapy.[117]

PPI therapy for EoE

The use of PPIs in the management of EoE has been one of the biggest advances in the short life of EoE.[118] Over the course of just one decade, these drugs initially developed to inhibit acid gastric secretion, have evolved from being an instrument to rule out GERD as a cause of esophageal eosinophilia,[38] to the defining factor of PPI-responsive esophageal eosinophilia (a provisional condition now recognized as true EoE[119]) and, finally, to constitute an anti-inflammatory treatment for EoE.[1] Beyond its antisecretive properties, an effect in downregulating esophageal gene expression of eotaxin-3/CCL26 and Th2 cytokines interleukin (IL)-5 and IL-3 in biopsies from patients with EoE was found for PPI, similar to that of patients treated with topic corticosteroids.[120] These drugs also restore the integrity of the damaged esophageal mucosa among patients who respond to treatment,[121] and reverse the inflammatory transcriptome.[122] PPIs also reverse fibrous remodeling in patients with EoE, restoring fibrotic features in endoscopy and esophageal distensibility.[123] All these effects of PPI in EoE are independent of inhibition of gastric acid secretion,[124] and add to the antioxidant properties previously described for PPIs to their direct effects on inflammatory and epithelial cells that could prevent inflammation.[125]

The effectiveness of PPI therapy to induce symptomatic and histological remission of EoE has been demonstrated in multiple observational studies, mostly based on case series, with both prospective and retrospective elements, and involving patients of all ages. The 33 studies available up to 2016 were summarized in a systematic review with meta-analysis[76] which provided evidence that PPIs given at double doses led to histological remission (defined as <15 eos/hpf) in 50.5% (95% CI = 42.2–58.7%) and symptomatic improvement in 60.8% (95% CI = 48.38–72.2%) of patients, irrespective of patient age, study design, or type of PPI evaluated. In addition, PPI effectiveness to induce remission of EoE was independent of the presence of pathological exposure to acid, demonstrated by esophageal pH-metry. Subsequent data provided evidence on the effectiveness of PPI in maintaining remission. In children, a prospective series showed that 78% remained in remission after 1 year with half the dose used for induction.[126] In adults, PPIs at half the initial dose maintained clinical and histological remission in at least 75% of patients after at least 1 year of follow-up.[124,125-128] Notably, dose escalation recovered remission in most relapsing patients, thus demonstrating PPI as a suitable first-line therapy to induce and maintain remission in 50% of patients with EoE. Evidence-based guidelines published in 2017 first recommended PPI as a cheap, accessible, and convenient therapy with moderate effectiveness in treating EoE;[1] an international consensus document supported this recommendation in 2018,[119] and placed PPI as a first-line option for the treatment of EoE in patients of all ages, at the same level as swallowed topic steroids and elimination diets. At present, there are no reported safety concerns for PPI therapy in EoE; indeed long-term safety studies in adults who have used PPI in standard doses for between 5 and 12 years have shown no significant side effects.[129] Definitive data on the long-term safety of PPI therapy in children have yet to be provided.[130]

Recommended PPI doses to induce EoE remission in adults are omeprazole 20–40 mg twice

daily or equivalent, and in children 1–2 mg/kg of omeprazole daily or equivalent. This medication is recommended to be used for at least 8 weeks, and effectiveness should be assessed with the aid of endoscopy with biopsies. A non-significant trend toward greater efficacy was observed when the daily dose was divided into two intakes. The drug should be used also to maintain disease remission in the long term in EoE patients with an initial response to PPI therapy, as discontinuation leads to symptomatic and/or histological relapse. The long-term strategy is to use the minimal effective dose to maintain remission, usually standard PPI doses. According to surveys carried out in different clinical settings,[44,131–134] this has made PPI the most commonly prescribed initial therapy to treat patients with EoE of all ages.

At present, no randomized trial has compared the effectiveness or safety of PPI with other treatment options, and it is not expected that we will have such a study soon. Hence, the most solid demonstration of the effectiveness of PPI in real-world practice has been provided by the EoE CONNECT registry, a European collaborative research project based on data registered by collaborators at 40 study sites. After analyzing data from 630 patients (including 76 children) treated with different PPI drugs at several dosages, it was confirmed that, overall, PPI therapy reduced eosinophil density below the diagnostic threshold of 15 eos/hpf in 48.8% of patients, with 37.9% of patients achieving $\leqslant$5 eos/hpf. Regarding clinical response, PPI therapy induced symptomatic improvement in 71.0% of patients.[135] PPI treatment was most effective in achieving clinico-histological remission of EoE when used in double or higher, rather than standard or lower, doses (50.8% *versus* 35.8%), and when the duration of therapy was prolonged from 8 to 12 weeks (50.4% *versus* 65.2%). However, additional benefit was not found with treatment length over 12 weeks. In addition, no significant differences were found among the different PPI drugs in achieving clinico-histological remission when used at double doses. Further increases to quadruple doses did not improve remission rates. Finally, no significant differences were noted among the different PPI drugs when used at equivalent doses.

Among patient responders to PPI, a reduced dose from that used for induction was effective in maintaining EoE in histological remission ($<$15 eos/hpf) in 69.2%, with 59.6% of them having $<$5 eos/hpf. With regarding to symptoms, 72.4% of patients under standard or lower doses of PPI maintained clinical remission. An EoE stricturing phenotype, by presence of fibrotic changes at baseline endoscopy (rings and/or strictures), was identified to significantly reduce the effectiveness of PPI as a first-line therapy and also tended to reduce its effectiveness to maintain remission, thus indicating that patients with a reduced esophageal caliber at baseline should be better treated with STCs.

Dilation

Long-standing untreated eosinophilic inflammation in EoE may progress into developing esophageal strictures, which constitute one of the most severe complications of EoE. As esophageal narrowing is frequently under-detected during endoscopy in patients with EoE when compared with barium esophagram,[136] the prevalence of clinically relevant fibrostenosing EoE is underestimated in regular practice. Patient age and delayed diagnosis are recognized as determining factors for a fibrotic and stricturing EoE phenotype: For every 10-year increase in patients' age, the odds of having a fibrostenotic EoE phenotype at diagnosis doubled.[8] The association between a delay in diagnosis with stricture formation has been independently demonstrated in adult cohorts from Switzerland and the United States: the prevalence of fibrotic features of EoE, based on endoscopy, increased from 46.5% to 87.5% when the diagnostic delay, respectively, was 0–2 years or more than 20 years from symptoms onset.[7] The esophageal diameter (determined as the smallest esophageal dilation bougie with moderate resistance during dilation) was $<$10 mm in patients with 15 years diagnostic delay, but $\geqslant$17 mm when it was only 5 years.[9] Esophageal strictures are less commonly found in pediatric cases of EoE, most likely due to the limited progression of the disease. In addition, esophageal narrowing in children more commonly involves an inflammatory component that responds well to anti-inflammatory medical treatment;[137,138] therefore esophageal dilation is usually reserved for selected cases.[139,140]

Esophageal dilation with through-the-scope hydropneumatic balloons and Maloney or Savary bougies has been employed as a treatment option for EoE patients from the earliest documented cases; it is used in a similar way in rigid or fibrous

esophageal strictures resulting from prolonged GERD or after the ingestion of caustic substances.

A meta-analysis of 27 studies that summarizes all the published evidence on endoscopic dilation up to 2016 demonstrated esophageal dilation provided any immediate improvement of dysphagia in 95% of patients following the procedure (95% CI = 90–98%).[141] However, this improvement could not be quantified since most of the source studies included in this analysis provided no details on changes in symptom scores after dilation, but rather a dichotomous outcome response (improvement of dysphagia: yes or no) was used. The fact that some patients undergoing dilation also were receiving concomitant drug[6,142] or diet-based[139,143] anti-inflammatory therapy obscures the clinical effect of the endoscopic therapy itself.

No differences in the effectiveness of dilation depending on the dilation device have been reported; therefore, symptomatic improvements can only be attributed to the increase induced in the esophageal caliber. The objective post-procedural esophageal caliber in adolescent and adults has been reported to be at least 16 mm, a measurement that relieves dysphagia and avoids food impaction.[141,144] This target diameter can be achieved in one session or after gradual dilation over several sessions, depending on the initial esophageal caliber and the effect noted during dilation.

No major safety concerns were associated with esophageal dilation, as complications were rare, and similar to those described in benign esophageal strictures of other etiology.[145,146] They included perforations in 0.38% (7/1831 dilation procedures), hemorrhage in 0.05% (1/1746 dilation procedures), and hospitalization in 0.67% (12/1777 dilation procedures), with no deaths reported in the source studies. Dilation is also safe among pediatric EoE patients, as shown by a single-center series of 68 children who were dilated over a 5-year period:[143] Chest pain was reported in 14.7% of EoE dilation, which was not related to dilation method, final dilator size, concomitant medical therapy, or esophageal eosinophilia. No perforations or significant hemorrhage were reported.

The early literature reported mucosal tears or disruptions which appeared in up to 22% of procedures, as a complication of endoscopy in EoE.[147,148] However, this feature is now considered as an indication of adequate endoscopic dilation and demonstration that an esophageal stricture has been solved. The appearance of a mucosal tear should end a session of endoscopic dilation, since going further could increase the risk for esophageal perforation.

Despite esophageal dilation constituting an effective and safe treatment in adult and pediatric EoE patients,[144] it has no effect on the underlying eosinophil inflammation; therefore, repeated dilation has been required to keep patients symptom-free when it is used as a single treatment for EoE.[6,149] To add an effective drug or dietary-based EoE therapy has been shown to reduce significantly the need of further dilation,[150] and to increase the esophageal caliber with no need of further dilation interventions,[123,151] therefore it should be recommended in all patients with a stricturing EoE phenotype.

An RCT has demonstrated that endoscopic dilation provides no further benefit to patients with no esophageal strictures at the time of diagnosis beyond that of anti-inflammatory therapy with effective PPI or STC treatment,[152] and treatment with fluticasone propionate (followed by esophageal dilation if required) has been shown to be more cost-effective than dilation first in patients who continue to be symptomatic despite PPI therapy.[153] Therefore, esophageal dilation should be considered in three clinical scenarios: (a) in patients with fibrostenosing EoE at the time of diagnosis, (b) in patients who have symptoms of EoE (dysphagia/food impaction) and persistent esophageal strictures after other measures have failed, and (c) in case of persistent dysphagia in the presence of endoscopic and histological remission with medical or dietary therapy.

A glimpse into the future: novel therapies for EoE under investigation

A variety of novel targeted therapies, some of them imported from bronchial asthma and atopic dermatitis, are currently being investigated in EoE. Late-phase clinical trials with monoclonal antibodies targeting IL-13 (cendakimab), IL-4 (dupilumab), the alpha subunit of the IL-5 receptor (IL-5Rα; benralizumab), and Siglec-8 blockers (Lirentelimab) will soon provide evidence of the potential of these molecules to control, not

only eosinophilic inflammation and esophageal symptoms but also some concomitant atopic manifestations these patients commonly present.[36] Non-biological, oral administered therapies for EoE are also promising. Among those, modulators of the sphingosine-1-phosphate receptors (S1PRs) are promising drugs, which are being evaluated to treat several immune-mediated diseases, including inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, and psoriasis.[154] The safety and effectiveness of etrasimod (APD334), a selective ligand of S1P1R1, S1PR4, and S1PR5, is currently being studied in EoE in a phase II RCT (ClinicalTrials.gov Identifier NCT04682639). Finally, as intercellular signals produced by the interactions of Th2 cytokines with specific receptors are transduced through the Janus kinase (JAK), which phosphorylates signal transducer and activator of transcription (STAT) factors, the JAK-STAT pathway has been identified as a potential target in the treatment of EoE. Although no study is yet formally planned in EoE, the effectiveness of the JAK inhibitor tofacitinib to induce clinical and endoscopic remission and to significantly reduce esophageal eosinophilic infiltration in a patient with all treatment-resistant EoE has already been reported.[155]

Therapeutic algorithm in EoE: just applying the evidence

Currently, PPIs, diet, or topical steroids might be offered to patients as first-line anti-inflammatory therapy. 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. Several surveys on clinical practice[44,131–133] and extensive case registries[134] have shown that, despite being one of the least effective therapies, PPIs constitute the most widely used first treatment option for EoE, due to their accessibility, safety, and low cost. They are not suitable, however, for patients with a structuring EoE or those with severe symptoms. The effectiveness of any therapy should be checked by a follow-up endoscopy with esophageal biopsies after a 6- to 12-week initial course. Second-line therapy choice is made easier when a patient does not respond to the first-line therapy, thus restricting the available options. Evidence that extended food elimination diets and PPI therapy up to 12 weeks has been provided.[135,156] Dietary therapy is the only drug-free option that targets the primary cause of EoE; 2-FED and 4-FED are preferable options, with milk-free diets being considered for young children. Responders to any empirical diet must reintroduce, one at a time, all excluded food groups, with an endoscopy following each introduction. The final goal is to provide a personalized maintenance therapy, with long-term removal only of food triggers. Patients should be aware that two or more foods can be involved in triggering EoE, making long-term adherence to the diet more difficult. These patients could benefit from dietary and nutritional advice.

STC is probably the most efficient anti-inflammatory option for EoE, as they have a good safety profile and have been seen to be useful in inducing and maintaining disease remission. When available, specific formulas designed to target the esophageal mucosa are preferred; BOTs seem to offer the best effectiveness to lowest dose ratio.

At this time, there is no evidence that the combination of two or more therapies enhances the individual efficacy of either, so the use of more than one option simultaneously should be discouraged; if EoE remission were achieved, it would be difficult to know which of the therapies had been responsible and should therefore be maintained in the long term.

Once an effective therapy is instigated, disease remission should be maintained using the same option at the minimum effective dose (in the case of PPI or STC) or dietary restriction level. A therapeutic choice might be changed over time where there are treatment side effects or patient's unwillingness to continue with medication or diet (including a potential negative impact on HRQoL of life and family resources). No common agreement exists regarding the methods and frequency of patient follow-up once in remission, but monitoring of symptoms should be continued at least. Periodic endoscopy and biopsy should be considered at individual patient level.

The proposed therapeutic algorithm for EoE is summarized in Figure 1. By applying the currently available options, optimizing their use, and combining them with endoscopic dilation in the event of stenosis or persistence of symptoms despite histological normalization, it is now possible to successfully control a large proportion of

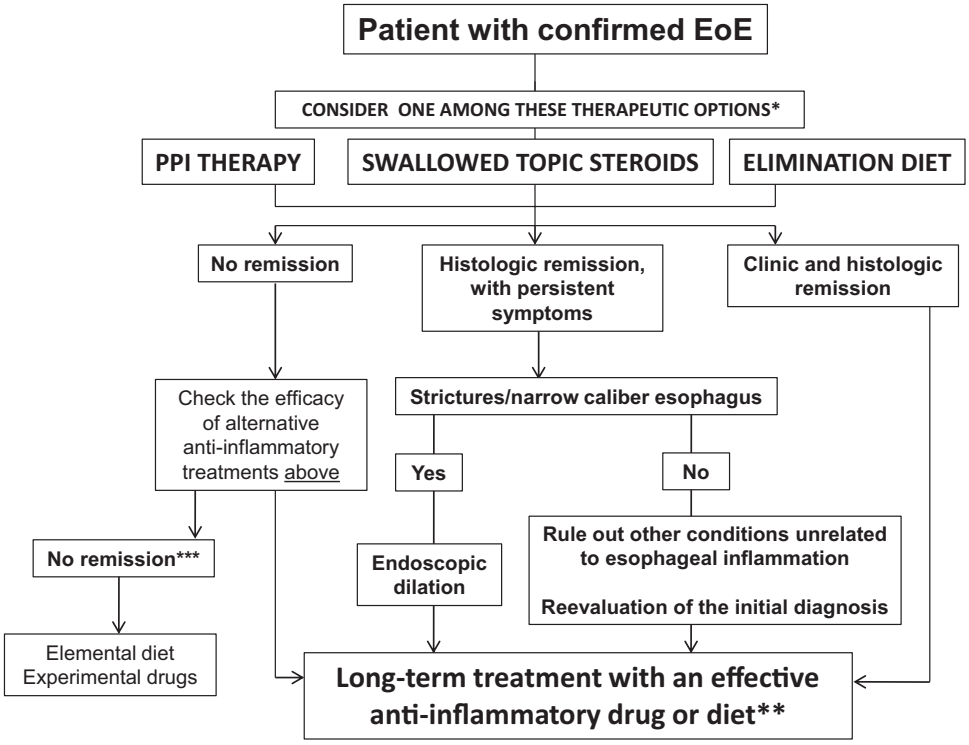

Figure 1. Evidence-based therapeutic algorithm proposed for treating eosinophilic esophagitis in clinical practice.

patients with EoE. For non-responders, there is intense research underway developing: new STC formulations designed to optimally coat the esophageal mucosa, systemic biological drugs against various therapeutic targets, and small molecules that interfere in the signaling pathways of the inflammatory response in EoE, all aimed at reducing the impact of the disease for sufferers and their families.

Author contributions

Sara Feo-Ortega: Investigation; Writing – original draft; Writing – review & editing.

Alfredo J Lucendo: Conceptualization; Investigation; Supervision; Writing – original draft; Writing – review & editing.

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