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Expert Review of Clinical Immunology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierm20

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Alfredo J Lucendo & Javier Molina-Infante

To cite this article: Alfredo J Lucendo & Javier Molina-Infante (2022): Current treatment options and long-term outcomes in patients with eosinophilic esophagitis, Expert Review of Clinical Immunology, DOI: 10.1080/1744666X.2022.2096591

To link to this article: https://doi.org/10.1080/1744666X.2022.2096591

EXPERT REVIEW OF CLINICAL IMMUNOLOGY
https://doi.org/10.1080/1744666X.2022.2096591

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REVIEW

Current treatment options and long-term outcomes in patients with eosinophilic esophagitis

Alfredo J Lucendo [a,b,c,d] and Javier Molina-Infante [b,e]

[a]Department of Gastroenterology, Hospital General de Tomelloso, Tomelloso, Spain; [b]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain; [c]Instituto de Investigación Sanitaria de Castilla-La Mancha (IDISCAM), Spain; [d]Instituto de Investigación Sanitaria La Princesa, Madrid, Spain; [e]Department of Gastroenterology, Hospital Universitario de Caceres, Caceres, Spain

ABSTRACT

Introduction: Dietary and pharmacological (proton pump inhibitors, swallowed topical corticosteroids) therapies are effective for induction of clinical and histological remission of eosinophilic esophagitis. However, data evaluating their long-term efficacy and safety is limited.

Areas covered: Since eosinophilic esophagitis is chronic, clinical, endoscopic, and histological features usually recur when successful treatments are stopped. In untreated patients, persistent esophageal eosinophilic inflammation may progress to fibrostenosis over time, giving place to strictures and narrow-caliber esophagi. This article comprehensively reviews available data on long-term maintenance of eosinophilic esophagitis with pharmacological and dietary treatment. It also discusses limitations re: available literature and outlines data gaps on adherence to therapy and monitoring disease activity in the long-term.

Expert opinion: Evidence indicates that long-term maintenance therapy may decrease the risk of esophageal stricture, food bolus impaction, and need for dilation in patients with eosinophilic esophagitis. Further knowledge on eosinophilic esophagitis phenotypes is needed to ascertain who will benefit best from sustained therapy. Unanswered questions include an adequate definition for sustained remission, best strategies for maintenance drugs and diets, enhancement of treatment adherence, and proper monitoring for long-term surveillance.

ARTICLE HISTORY
Received 5 March 2022
Accepted 28 June 2022

KEYWORDS
Budesonide; diet therapy; dilation; eosinophilic esophagitis; fluticasone; food elimination diet; food hypersensitivity; formulated food; long-term care; proton-pump inhibitor; swallowed corticosteroids

1. 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 results from an immune-mediated response mainly against dietary antigens [3].

With the first cases being described during the 1980s, EoE was first characterized as a distinct clinical-pathological syndrome less than 3 decades ago [4,5]. Since then, the epidemiology of EoE has increased dramatically, becoming the most prevalent cause of chronic esophageal symptoms in children and adults – up to their 5th decade of life – in developed countries [6,7]. In the absence of treatment, the symptoms of EoE tend to persist over time [8], causing psychological distress [9] and impacting on social activities that revolve around food [10], thus worsening patient quality of life [11,12] and, in the case of the youngest patients, also that of their families [13]. At the same time, the chronically maintained inflammation of the esophagus in EoE patients generates tissue changes that lead to collagen deposition in the deeper layers of the organ [14], and fibrous remodeling that leads to the formation of rings, strictures, and narrow-caliber esophagus [15]. Patients with active EoE are also at risk of complications, with esophageal perforation following food impaction being potentially the most serious [16]. All of the above clearly indicates the need to treat patients with active EoE. Due to its chronic nature, the symptoms and esophageal inflammation recur after discontinuation of any treatment [17], so treatment should be seen as a long-term strategy for most patients [18].

The first therapeutic interventions for EoE were tested in pediatric patients shortly after the characterization of the disease – when it was identified as a particular form of food allergy by demonstrating the disappearance of esophageal eosinophilic infiltrate and symptoms after avoiding most common foodstuffs and replacing them with an exclusive elemental diet devoid of antigens [3]. The disease recurred rapidly in all cases after returning to a normal diet. Shortly after, the administration of topical corticosteroids, swallowed rather than inhaled in order to reach the esophageal mucosa, demonstrated comparable efficacy to oral systemic corticosteroids [19], but significantly fewer adverse events [20]. Proton pump inhibitor (PPI) drugs joined the therapeutic arsenal for EoE more recently, after doubts about their position in the diagnostic-therapeutic algorithm and their potential relationship with gastroesophageal reflux were resolved [21]. Currently, the investigation of new drugs for the treatment of EoE is one of the fastest growing areas in digestive diseases, with the first of these specific drugs already being available in some clinical settings [22].

CONTACT Alfredo J Lucendo ajlucendo@hotmail.com Department of Gastroenterology, Hospital General de Tomelloso, Vereda de Socuéllamos s/n 13700, Tomelloso, Spain

Article highlights

- EoE is chronic condition in which symptomatic, endoscopic, and histological disease activity recurs when successful treatments are stopped.
- Mounting evidence suggests that left untreated, persistent eosinophilic esophageal inflammation progresses to fibrous remodeling over time, giving rise to structures and narrow-caliber esophagus. Therefore, maintenance therapy in EoE is strongly recommended.
- Knowledge about EoE phenotypes is limited. A relevant proportion of patients show a mild non-progressive clinical and endoscopic pattern. Elucidating who will and who will not benefit best from maintenance therapy remains one of the most relevant unresolved issues.
- Currently available therapies that have been proven to achieve remission in EoE include diet, PPIs and swallowed topical corticosteroids. All of these therapies have also demonstrated effectiveness in maintaining disease remission in the long term.
- Unlike induction therapy, data on the effectiveness of the different maintenance therapies is scarce, generally coming from observational studies and with a certain risk of bias.
- The same treatments used to induce EoE remission have been shown to be effective in maintaining it in the long-term. As they have generally been used at lower doses, probably suboptimal, the efficacy has been shown to be less than that for induction.
- Key unanswered questions include how to define sustained remission, the best strategies to maintain it and ensure treatment adherence, and optimal surveillance methods for its monitoring.

The efficacy of different therapies to induce clinical and histological remission in patients with EoE has been defined through several systematic reviews with meta-analyses [23–25]. However, the effectiveness and safety of each therapy in maintaining a chronic, most likely lifelong disease, such as EoE in long-term remission has been little evaluated. Available data to answer this question is more scarce, frequently dispersed in the literature and poorly systematized.

This paper aims to provide an overview on the ability of currently available therapies to induce and maintain long-term remission in EoE patients of all ages.

2. Topic corticosteroids in EoE: the best studied option, but not in the long term

Current United European Gastroenterology evidence-based guidelines recommend either elimination diet, double-dose PPI or swallowed topical corticosteroids (STC) for the initial treatment of EoE [1]. In fact, corticosteroids with reduced bioavailability, swallowed instead of inhaled, were proved to be as effective as orally administered systemic corticosteroids in inducing clinical and histological remission of EoE in a randomized-controlled trial (RCT) [20]: Eighty pediatric EoE patients were allocated to either inhaled topical fluticasone (which was applied over the tongue and then swallowed) or oral prednisone; a similar proportion of patients in both groups presented histological improvement, despite prednisone producing a greater degree of eosinophil reduction. All patients treated with fluticasone and prednisone were free of symptoms at week 4 of therapy. However, there was a relapse in 45% of patients after 24 weeks of treatment cessation, with no differences between drugs in terms of relapse rate or time to relapse. Systemic adverse effects were significantly more frequent in patients allocated to the prednisone arm [20].

2.1. Swallowed topic corticosteroids to induce remission of EoE

Over the years, multiple clinical trials with STC have been carried out, promoted by both independent researchers and by pharmaceutical companies. These have mainly compared different formulations of budesonide [26–29], fluticasone [30–32] and, to a lesser extent, beclometasone [33] and mometasone [34] in different forms of esophageal delivery with placebo or esomeprazole, for induction of histological and clinical remission of EoE. Their results have been summarized in several systematic reviews with meta-analyses, showing that STC were significantly more effective than placebo in inducing histological response for both complete (OR 35.82, 95% CI 14.98 to 85.64) and partial response (OR 28.44, 95% CI 8.56 to 94.47), according to the most recent summary [25]. Moreover, STC were useful in achieving clinical response (OR 2.53, 95% CI 1.14 to 5.60) and endoscopic improvement (OR 3.51, 95% CI 1.47 to 8.36). SCT presented an adequate safety profile, the most common adverse event being esophageal candidiasis (mild in most cases and did not require discontinuation of treatment). No increased risk of adrenal suppression was observed compared to placebo [35]. Table 1 provides details on dose ranges and specific instructions for administration of topical steroids in patients of all ages with EoE.

Despite STC being clearly superior to placebo overall, a wide heterogeneity was identified among the different studies in terms of effectiveness. The potency of action of budesonide and fluticasone has been seen to be comparable [36,37], but the method used to deliver the drug over the esophageal mucosa has been shown to be essential to ensure its therapeutic effect. This was demonstrated in 2012 by a RCT that compared oral viscous budesonide to nebulized budesonide given at the same dose: The viscous solution produced a higher reduction in peak eosinophil counts in esophageal biopsies and normalization of endoscopic appearance of the esophagus. As a consequence, it provided better coverage of the internal esophageal surface and longer contact time between the drug and the mucosa [38].

However, the different formulations of viscous budesonide, produced by mixing this compound with varying solutions to deliver the medication into the esophagus (including hypoallergenic food powder, cocoa mix, pear sauce, xanthan gum, and rice cereal) [39,40], are not comparable, and the literature has described widely variable efficacy among them [41]. To minimize this and ensure predictable results, some companies have developed standardized formulations of budesonide, including TAK-721, an investigational budesonide oral suspension (BOS) to treat adolescents and adults with EoE [26] and a budesonide orodispersible tablet (BOT) [27]. The latter has been approved by the European Medicines Agency and is already available in several countries. A recent network meta-analysis identified the BOT 1 mg twice daily as the best treatment option to induce remission in EoE in adult patients. It was the most effective compared to all the available drug therapies investigated in RCTs up to 2020 [42], including viscous formulations of any topical corticosteroids and even monoclonal antibodies targeting interleukin (IL)-5 and IL-13.

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

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

[a]If an inhaler is used, the patient should be instructed to puff the medication directly into their mouth without using a spacer during a held breath.
[b]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.
[c]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.
[d]Oral viscous budesonide preparation consists of mixing 1–2 mg budesonide with 5 mg of sucralose or similar.
[e]Specific doses in children will be determined by age, height, or weight.
[f]Available in several European countries, the daily dose is divided into two intakes.
[g]Four doses of 50 micrograms applied orally by spray 4 times daily.
[h]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.
[i]Provided at inhalation aerosol 80 µg per puff, 2 puffs swallowed twice a day.

The potential advantage of a tablet formulation, compared to a viscous suspension of budesonide, could partially be due to how they are conducted through the esophagus, with the latter still requiring a certain volume, while the former uses the saliva itself secreted by the effervescent stimulus of the tablet. Bearing in mind that the esophagus is a muscular organ with the function of quickly conducting boluses to the stomach and that its capacity is only virtual, a smaller volume of solution (the secreted saliva itself) could be an advantage. Based on this assumption, a new orodispersible tablet for EoE containing fluticasone is currently under development, with promising results for the 3 mg once daily dose, according to a recently published phase 2 RCT [32].

2.2. Long-term effectiveness of topical corticosteroid therapy in EoE

Relapses of EoE are frequently observed once treatment has been discontinued [17,43], even if profound histological remission has been achieved and maintained for a long time [17,44]. Furthermore, an increased use of STC during follow-up has been found to be associated with a lower risk for bolus impaction [45]. During this period, structured follow-up must be ensured for all patients with EoE, as in any other chronic disease, and clinical practice guidelines recommend maintaining long-term remission using the minimum effective doses of the drugs that were used to induce remission [1].

To date, a total of 3 RCTs [46–48], 2 open-label prospective studies [49,50] and 3 retrospective observational studies [44,51] have evaluated the efficacy of STC in maintaining remission in patients who took this medication on a continuous basis: two studies were carried out in pediatric populations (Table 2). In all of these studies, patients had clinical and histological remission of EoE at baseline (although variable criteria were defined in the different studies). Studies analyzing STC intermittently are not considered here.

Most studies used half the STC dose that had been effective in inducing remission to maintain remission, either budesonide (administered in a viscous formulation in most cases) or fluticasone powder from a metered-dose inhaler for asthma, applied orally and swallowed, and in all cases divided into two intakes.

The duration of the maintenance therapy with STC ranged from 12 weeks to 5 years. Taken together, currently available data supports STC as being effective in maintaining long-term remission in EoE, but remission rates were lower than those observed after induction therapy. With the exception of one trial that used BOT [47], no study in adults was able to maintain histological remission in more than half of its patients. The results in children were somewhat better. Higher STC doses generally improved maintenance of remission results. Best rates of remission maintenance were provided by BOT, which, at either 0.5 mg or 1 mg twice daily, was able to maintain disease remission in more than ¾ of patients.

After discontinuation of treatment (including allocation to placebo in RCT), rapid relapse was seen in most patients (approximately within a 3-month period). Therefore, treatment discontinuation cannot be recommended in patients with EoE who are properly controlled with therapy and present no signs of intolerance or adverse events.

Both low and high-dose of STC were well tolerated, with an excellent safety profile, no signs of adrenal suppression and with limited cases of esophageal candidiasis (this was easily treated with fluconazole in most cases with no need for STC withdrawal).

3. Proton pump inhibitor (PPI) therapy

PPIs are often the first drug of choice worldwide in EoE because they are inexpensive, easy to administrate and demonstrate a good safety profile [1,2,53,54]. Response to PPI therapy was initially linked to underlying gastroesophageal reflux disease (GERD), ruling out EoE [55]. However, a first prospective series in 2011 revealed that clinical, endoscopic, and histological features were not distinguishable between responders and non-responders to PPI therapy, whereas GERD could not be identified in a subset of

Table 2. Efficacy of swallowed topical corticosteroids for maintenance therapy after successful induction therapy.

Author, year	Design	Study population	Drug and mode of delivery	Treatment regimen	Treatment duration	Results	Comments
Straumann A, 2011 [46]	RCT	Adults (n = 28)	Budesonide suspension formulation	0.25 mg twice daily or placebo	50 weeks	35.7% of patients under budesonide but 0% under placebo maintained <5 eos/HPF. 50% of patients under budesonide but 71.4% under placebo had >20 eos/HPF	Additional histological features at end of treatment and blood analysis results were not different between groups. Differences in symptoms were not significant between budesonide and placebo. No patient presented candidiasis
Andreae DA, 2016 [49]	Open-label, prospective	Children (n = 54)	Fluticasone propionate metered dose inhaler, swallowed	2 puffs toswallow twice a day, containing 44 to 220 mcg per puff, depending on patient's age	mean ± SD 20.4 ± 1.7 months	63% of patients had <15 eosinophils /HPF at >24 months follow-up. 58% of patients had <5 eos/HPF at >24 months follow-up	The % of patients with symptoms improved significantly from baseline, but no patient-reported outcome instrument was used. Histological and endoscopic features significantly improved from baseline. Esophageal candidiasis appeared in 3 patients annually.
Eluri S, 2017 [51]	Retrospective	Adults (n = 33)	Budesonide aqueous formula mixed into aslurry with 5 g of sucralose,orfluticasone propionate metered dose inhaled, swallowed	0.5–1 mg twice daily, based on patient age 440–880 mcgtwice daily, based on patient age	median 11.7 months	39% maintained <15 eos/HPF 61% had histological loss of response to treatment.	Symptoms were not structurally assessed, No information on adverse events provided
Greuter T, 2019 [44]	Retrospective, single-center	Adults (n = 59)[a]	fluticasone powder from a metered-dose inhaler applied orally and swallowed) Budesonide syrup with a sucrose concentrationof 64%	0.25 mg twice daily 0.25 mg twice daily	median 5 (IQR, 3–7) years	49.2% patients had <15 eos/HPF	Symptomatic response not structurally evaluated No information provided on adverse events
Oliva S, 2019 [50]	Open-label, prospective	Children (n = 20)	Budesonide oral viscous formula	1 to 2 mg/day, depending on patient' age, divided into 2 doses	12 week	85% of patients maintained <6 eos/HPF	Most patients maintained a normal endoscopy No cases of oral or esophageal candidiasis were described, and no changes in serum cortisol from baseline were documented
Straumann A 2020 [47]	RCT	Adults (n = 204)	Budesonide orodispersible tablet	0.5 mg twice daily (n = 68)1 mg twice daily (n = 68), placebo (n = 68)	48 week	% of patients with <5 eos/HPF: 77.9% with 0.5 mg twice daily; 83.8% with 1 mg twice daily; 2.9% with placebo	Groups with active medication presented significant improvement in symptoms and quality of life from baseline. Five cases of confirmed candidiasis among patients under active drug
Greuter T, 2021 [52]	Retrospective, multicenter	Adults (n = 82)	Fluticasone metered dose swallowed (n = 60), budesonide oral suspension (n = 22)	Low dose: 0.5 mg/day (71%) High dose >0.5 mg/day (29%)generally divided into two doses	Median 2.2 (IQR,1.0–3.8) years	27.6% of patients under low dose STC maintained <15 eos/HPF 45.8% of patients under high-dose STC maintained <15 eos/HPF	40% received co-treatment with PPI. Esophageal candidiasis infection was seen in 3 (5.2%) and 2 (8.3%) patients in the low and high-dose groups, respectively
Dellon ES, 2021 [48]	RCT	Adolescents and adults (n = 48)	Budesonide oral suspension (TAK-721)	2 mg twice daily (n = 25); Placebo (n = 23)	36 weeks	52% maintained <6 eos/HPF under budesonide 31.3% maintained <6 eos/HPF under placebo	36% patients experienced histological relapse >15 eos/HPF under budesonide and 78.2% under placebo

RCT: randomized controlled trial; eos/HPF: eosinophils per high-power field; IQR: interquartile rank; STC: swallowed topic corticosteroids
[a]Only patients who were continuously treated with STC for 3 successive visits were considered.

EoE responders to PPI [56]. Since then, mounting evidence has demonstrated a significant baseline overlap related to features of Th2 immune-mediated inflammation [57] and gene expression [58] between responders and non-responders to PPIs. Furthermore, PPI therapy reduces Th2 inflammation [57], reverses the abnormal EoE gene expression signature [58] and curtails transcriptomic processes involving IL-13-induced responses [59], all similar effects to those exerted by topical steroids in EoE patients. Consequently, PPI therapy was unanimously accepted in a first-line therapy for EoE international position paper [60] and further included in European [1] and American [2] guidelines.

Updated evidence has shown that beyond reduction of acid production in patients with coexistent GERD, PPI therapy may benefit patients with EoE by either anti-reflux mechanisms (which mainly imply enhanced clearance in mid and distal esophagus, of either normal or pathological reflux, measured by esophageal impedance-pH monitoring [61,62]) or acid-independent in-vitro anti-inflammatory mechanisms [63]. Dose-dependent reduction of IL-13- and IL-4- induced eotaxin-3 expression by omeprazole in cells from EoE patients was first reported in 2013 [63]. Vonoprazan, a potassium-competitive acid blocker (P-CAB), which exhibits a more rapid, profound, and sustained acid suppression than PPIs, showed similar efficacy in terms of clinical, endoscopic, and histological remission in EoE patients from Japan when compared to PPIs [64]. Despite speculating that effectiveness of P-CABs (and PPIs) might be due exclusively to acid suppression, a recent experimental study on EoE cells proved similar aforementioned anti-inflammatory effects (decreased IL-4-stimulated eotaxin-3 secretion) for omeprazole and SCH 28080, which belongs to P-CABs [65]. In other words, acid suppressive effects for PPIs/P-CABs in EoE patients do not necessarily preclude concomitant in-vitro anti-inflammatory effects of PPIs/P-CABs. Further studies are necessary to elucidate the complex relationship between GERD, EoE, and PPI therapy.

3.1. Efficacy of PPI therapy for inducing EoE remission

In 2011, the first prospective study systematically evaluating response to PPI therapy in patients with suspected EoE revealed a 50% histological response – defined by <15 eosinophils per high-power field (eos/HPF) [56]. In the first meta-analysis published in 2016–33 studies with 619, mostly European and US, EoE patients – PPI therapy was associated with a 51% histological remission (<15 eos/HPF) [24]. A major limitation to this analysis, however, was the variability in response rates and significant heterogeneity between studies. In the first prospective study conducted in 51 Spanish children, 68% were found to have <15 eos/HPF after an 8-week high-dose (1 mg/kg/bid) PPI trial [66]. More recently, data from the EoE CONNECT registry on 630 European patients revealed histological remission in 49% of those included [67]. Finally, a recent retrospective study in 236 adult patients from Denmark disclosed histological remission in 49% of those treated with an 8-week high-dose PPI trial [68]. In conclusion, the vast majority of important studies over the past decade have reported consistent histological remission rates (<15 eos/HPF) of around 50% for PPI therapy in children and adults affected with EoE.

Several considerations should be made regarding optimization of PPI therapy for patients with EoE. In the above mentioned meta-analysis, PPIs seemed to be more effective when administered twice daily rather than once daily and when pathological acid reflux could be demonstrated [24]. Double doses (omeprazole 20 mg bid in adults, omeprazole 2 mg/kg bid in children) showed higher efficacy than simple doses [67]. No significant differences were found between equivalent doses of all available PPI formulations, although esomeprazole and omeprazole showed a higher tendency of effectiveness (54% and 56%, respectively) compared to pantoprazole, rabeprazole, and lansoprazole (46.3%, 38.9%, and 37.0%, respectively) in the EoE CONNECT registry [67]. It should be noted that extending treatment duration from 8 to 12 weeks resulted in higher clinical and histological remission (odds ratio 2.7, 95% CI 1.3–5.3) [67]. Similarly, an inflammatory phenotype predicted a better response (odds ratio 3.7, 95% CI 1.4–9.5), whilst a stricturing phenotype was associated with lower response rates both for induction and maintenance therapy [67].

3.2. Efficacy of PPI to maintain long-term remission

Several recent studies have shown notably consistent data on the long-term efficacy of maintenance PPI therapy, both in children and adults (Table 3). Regardless of the study population or different PPI maintenance doses or molecules, around three-quarters of initial responders to PPI therapy remained in clinical and histological remission on tapering maintenance PPI doses [66,67,69–71]. Most data came from endoscopic reassessment after 1-year maintenance therapy.

Limited data suggests that, over one year, most responders on maintenance therapy may keep in remission after re-tapering PPI doses. In a pediatric study, 11/12 patients (91%) were still in remission after lowering maintenance doses (from 1 to 0.5 mg/kg/day) for a further year [71]. As for adults, 15/18 patients (83%) were still in remission after re-tapering from 40 to 20 mg omeprazole once daily, although duration of therapy was not specified [70].

Table 3. Studies assessing the efficacy of maintenance PPI therapy after successful induction therapy.

Author,year of publication	Population	Samplesize	Maintenance PPI doses, duration	Efficacy (<15 eos/HPF)
Molina-Infante, 2015 [69]	Adult	75	Tapering PPI doses at the discretion of the clinician,1 year	73%
Gomez-Torrijos, 2016 [70]	Adult	38	Omeprazole 40 mg/day,1 year	81%
Gutierrez-Junquera, 2016 [66]	Children	14	1 mg/kg/day, 1 year	78%
Gutierrez-Junquera, 2018 [71]	Children	57	1 mg/kg/day, 1 year	70%
Laserna-Mendieta, 2020 [67]	Children and adult	103	Tapering PPI doses at the discretion of the clinician,not specified	69%

Interestingly, among adult initial PPI responders with relapsing esophageal inflammation >15 eos/PHF on tapering PPI doses, re-intensified PPI doses (omeprazole 40 mg twice daily) recovered histological response in 12/19 (63%) of patients [69]. Regaining of histological response was much more common in those patients with relapsing eosinophilia limited to the distal esophagus [69]. Therefore, a minimal proportion of initial PPI responders may require high-dose maintenance omeprazole in order to keep a sustained response.

Specific studies evaluating the safety of PPI therapy in EoE have yet to be published.

3.3. Predictors of sustained response to PPI therapy

a) Initial deep remission. Two recent studies have suggested that sustained remission on tapering PPI doses was more common in patients with initial deep remission on PPI therapy (<5 eos/HPF) as compared to those with partial remission (5–14 eos/HPF) (81% vs. 50%, p 0.01 [71], 73% vs. 50% p 0.11 [67]).

b) CYP2C19 genotype. CYP2C19 enzyme is the primary metabolic route for PPI molecules. Patients showing increased CYP2C19 enzyme activity (CYP2C19 ultra-rapid and rapid) might not have an adequate response to standard PPI doses due to a faster drug washout. A CYP2C19 rapid metabolizer phenotype is present in 50–70% people in Western populations [72]. An initial study in adults showed that loss of first response to PPI therapy was significantly more common in patients with a CYP2C19 rapid metabolizer phenotype (36% vs. 6%, p 0.01) [69]. These findings were corroborated in a pediatric study evaluating PPI therapy during the induction phase (rapid metabolizers had 8.2-fold better odds of failing to respond to PPI therapy) [73], but the same authors could not find a definitive association between response to tapering maintenance PPI doses and the CYP2C19 genotype in a further study [74]. Differences in molecules and dosing between studies, omeprazole being more sensitive and esomeprazole less sensitive to the effects of CYP2C19 genotype [69,73,74], may partially explain these conflicting results.

c) STAT6 variants. Emerging evidence has suggested that eosinophilic inflammation driven by STAT6-dependent local overexpression of eotaxin-3 can be altered by PPIs, through blockage of STAT6 binding and transcriptional activation of eotaxin-3 (8). In the aforementioned pediatric study, different STAT6 genetic variants were associated with response to PPI therapy during the induction phase [73]. More specifically, carriage of STAT6 allelic variant rs1059513 significantly predicted response to PPIs, whereas carriage of STAT6 rs324011 and a CYP2C19 rapid metabolizer genotype were predictors of lack of response to PPI [73]. As for maintenance PPI therapy, a very recent study from the same group confirmed an increased risk for early relapse on 1-yr maintenance PPI therapy in those patients carrying STAT6 variants rs324011, rs167769, or rs12368672 [74].

d) Esophageal microRNA. In another recent small pediatric study, esophageal (but not serum) microRNA levels (miR-664a-3p, miR-7-5p, miR-223-3p, miR-21-3p, and miR-375-5p) were able to discriminate at baseline between responders and non-responders to PPIs [75]. This promising tool warrants further validation in larger children and adult series.

e) Atopic rhinoconjunctivitis. Beyond CYP2C19 genotype, the first study in adults addressing long-term efficacy of PPIs showed that allergic rhinoconjunctivitis was a significant predictor of loss of response to PPI during follow-up (OR 8.6; 95% CI: 1.5–48.7) [69]. This study could not replicate this association for any other atopic comorbidity. Whether exposure to large or repeat allergen volume, or alternatively cross-reactivity, might amplify allergic Th2 immune, surpassing the responsiveness to PPIs threshold, remains unknown.

4. Dietary therapy

In 1995, eight children with refractory esophageal eosinophilia theoretically attributed to GERD, were successfully treated with an amino acid-based formula devoid of allergenic content (elemental diet) [3]. This seminal study was the first scientific evidence that EoE was a disease predominantly triggered by food antigens [3]. Since then, the role of food allergies in the pathogenesis of EoE has been demonstrated, based upon clinical and histological remission, after placing patients on various elimination diets. EoE is a unique and distinct form of non-immunoglobulin (Ig) E-mediated food allergy [76]; therefore, allergy testing-based elimination diets (eliminating foods with positive results on IgE-based testing – blood IgEs, skin prick testing – and non-IgE-based testing atopy patch testing) have met with limited success, especially in adults [23]. Failure of food allergy testing opened up the door to empirical elimination diets, which currently remain the gold standard for dietary therapy in clinical practice.

The main advantage of a diet approach is that it potentially offers an effective non-pharmacological treatment for induction and maintenance therapy. However, the most common food triggers worldwide are cow´s milk protein, wheat, and eggs [1], making strict avoidance of these food groups cumbersome in the long run. Highly restrictive diets, especially with coexisting IgE-mediated food allergies, eosinophilic gastrointestinal disorders, and relevant comorbidities, are at risk of failure and creating malnourishment in children [77–79]. In diet-treated EoE pediatric patients, avoidant/restrictive food intake disorder (ARFID) was first reported 3 years ago [80]. Both patients suffered from anxiety and food avoidance, despite histological remission and no other concomitant mental or physical comorbidity [80]. As for adults, recurrent food impaction (with disease and choking anxiety ranking highly) and dietary restrictions were demonstrated to be the most important factors influencing psychosocial domains in health-related quality of life [12]. All these facts stress the importance of adequate pre-selection of patient candidates for dietary therapy (aside from discussing initial minimally restrictive diets as a step-up strategy).

4.1. Efficacy of dietary therapy for inducing EoE remission

The efficacy of all available dietary strategies for inducing remission in pediatric and adult EoE patients is summarized in Table 4.

Table 4. Diet strategies available for pediatric and adult EoE patients, along with efficacy and main considerations for clinical practice.

	Efficacy(< 15 eos/HPF)		
	Children	Adults	Considerations
Elemental diet [23]	90%	94%	Poor palatability, extremely restrictive, psychosocial domains and quality of life impairment, high cost (not universally reimbursed)
Empiric 6-FED(milk, wheat, eggs, soy/legumes, nuts, fish/seafood) [23,81–83]	73%	71%	Highly restrictive. Numerous endoscopic procedures (6) after documenting response. Psychosocial domains and quality of life impairment. After stepping up from a 2- and 4-FED, all responders to a 6-FED were found to have 3 or more food triggers, which makes it cumbersome as maintenance therapy
Empiric 4-FED(milk, wheat, eggs and soy/legumes) [85,86]	60%	46%	Moderately restrictive. Numerous endoscopic procedures (4) after documenting response. Legumes beyond soy are more common as food triggers in Mediterranean countries. 80–90% patients were found to have 1 or 2 food triggers, which makes them best candidates for maintenance therapy
Empiric 2-FED (milk and wheat) [87]	44%	40%	Single study requiring external validation. Eggs might be more common than wheat as food trigger in other geographical settings. All patients were found to have 1 or 2 food triggers, which makes them best candidates for maintenance therapy
Allergy testing-directed elimination diet [23]	48%	32%	Consistent low efficacy in adult studiesConflicting results in pediatric studies, more effective in young children, methodological issues is some studies (response defined by symptoms, not by histological re-assessment)
Empiric 1-FED (milk)elimination diet [84,86,88]	51%*	25**	*Methodological issues with all available studies in children, even prospective (concomitant PPI therapy, selection bias) **Indirect data from adult patients responders to a 2- and 4-FED

FED: food elimination diet; eos/HPF: eosinophils per high-power field

4.1.1. Elemental diet

An elemental diet consists of exclusive feeding with a single amino acid-based formula, devoid of antigenic capacity. By far, it is the most effective dietary approach, with histological remission in over 90% of children and adults, according to a recent first meta-analysis [23]. However, this dietary strategy has a number of setbacks. These include poor palatability, psychosocial disadjustment and impairment of quality of life due to complete avoidance of any table food, as well as the cost implications of supporting such a strategy (often without reimbursement). Potential therapeutic roles for this extremely restrictive diet may include refractory patients who wish to be kept in remission while addressing the casual role of unusual allergens, or as a bridge therapy while waiting for investigational drugs.

4.1.2. Allergy testing-guided elimination diet

Allergy testing-based elimination diets have been commonly based on a combination of skin prick (measuring IgE-mediated food reactions) and atopy patch testing (measuring non-IgE-mediated food reactions) in order to design an individual-based diet by eliminating those foods with positive results. In the aforementioned first meta-analysis [23], histological remission results were lower than expected in children (48%, with variable results), whilst in adult patients it was consistently low (32%). Of note, milk, the most common EoE trigger, had the poorest predictive values using this food allergy testing. Therefore, current therapeutic guidelines concluded that the diagnostic accuracy of skin allergy tests remains insufficient to design effective diets for EoE patients.

4.1.3. Empirical elimination diet

In 2006, an empirical diet consisting of eliminating six food groups (milk, wheat, eggs, soy/legumes, nuts, fish/seafood), which accounted for the majority of food reactions in children from Chicago, led to complete histological remission in 3 out of 4 pediatric patients with EoE [81]. After validation of these initial pediatric results in two big studies in adults [82,83], the so-called six-food elimination diet (6-FED) became the standard for dietary therapy in clinical practice. Unfortunately, it became unpopular among patients and physicians, mainly due to a need for numerous endoscopic procedures and its high level of food restriction. Individual food reintroduction in patients who achieved histological remission with a 6-FED, each followed by an endoscopic procedure, led to identification of specific causal food antigens in EoE [84]. Cow's milk (especially in children <10 years-old), wheat and eggs, and to a lesser extent, soy, and legumes, were the most common food triggers for EoE in both children and adults [84]. Nuts, fish, and seafood played a negligible role as food triggers for EoE.

This was the rationale basis for developing a four-food elimination diet (4-FED) – eliminating the four more common food groups triggering EoE. This hypothesis was first tested in a Spanish multicenter study, in which a 4-FED diet led to histological remission in 54% of 52 adult EoE recruited patients [85]. Notably, milk and wheat of both were demonstrated to be the triggering foods in half of the responders to a 4-FED diet. After this first milestone, a multicenter study conducted in 78 children from the US demonstrated an even higher histological remission rate (64%) [86]. It is of note that 55% of pediatric responders to a 4-FED diet had cow´s milk as the only food trigger after individual food reintroduction. Therefore, both 4-FED studies demonstrated that approximately half of the responders had actually only one or two food triggers (primarily cow's milk and wheat), and so could have been potentially identified by starting with an even simpler approach: a two-food elimination diet (2-FED), withdrawing cow's milk and wheat.

This step-up approach was first assessed in 2018 in the biggest multicenter study conducted so far for diet in EoE, which gathered 130 consecutive adult and pediatric patients from 14 centers, mostly in Spain [87]. In this study, all patients underwent a 2-FED (cow's milk and wheat) and non-responders were offered an escalation to a 4-FED and eventually a 6-FED, if histological remission (<15 eos/HPF) was not

observed (2-4-6). Both clinical and histological remission were present in 43% of EoE patients undertaking a 2-FED. After escalating non-responders to a 4-FED, and ultimately to a 6-FED, efficacy rates were similar (60% and 79%, respectively) to those reported previously [23,81,86]. This step-up approach resulted in advantages compared to a top-down strategy (i.e. starting with a 6-FED), namely: eliminating unnecessary dietary restrictions (43% of included EoE patients were able to identify their causative foods while consuming legumes, eggs, fish/seafood and nuts, and up to 60% did not withdraw nuts and fish/seafood from their diet at all); a reduction of endoscopic procedures, and shortening the diagnostic process time by 20%. In addition, only 1 or 2 causative food groups were present in up to 90% of responders to a 2-FED or a 4-FED, leading to prompt identification of responders with few food triggers, without the disadvantages of a 6-FED. Undoubtedly, these patients are the best candidates for maintenance therapy with dietary interventions.

As such, a step-up empirical elimination diet, starting from one or two food groups, remains the current gold standard for a dietary approach in pediatric and adult EoE patients. In addition, a further computer-based simulation model found a 1–3 and 2–4 step-up approach to be an easier and more efficient strategy [88]. A further development of note is a recently published first multicenter prospective study evaluating the efficacy of a single-food milk elimination diet for EoE in children [89]. This approach led to histological remission in half of the patients, although up to 88% were also on PPI therapy (despite being non-responders to an initial PPI trial, according to current guidelines) [83]. Co-therapy with PPIs casts doubt on whether partial responders to PPIs were included, or synergistic effects between diet and PPIs were responsible for the study's notable efficacy. This aside, this study opens up the possibility of even simpler initial dietary approaches in children.

Unlike responders to a 2-FED or a 4-FED, responders to a 6-FED, with previous failure to a 2-FED and 4-FED, were shown to have three or more food triggers [87]. The higher the level of restriction step-up, therefore, the higher likelihood of having more food triggers. Long-term avoidance of causative, multiple triggering foods can be burdensome and even unfeasible, and therefore can result in non-adherence. As such, a 6-FED might be discouraged within the step-up strategy, or merely reserved for highly motivated patients who do not wish to take medication and/or are still willing to identify their food triggers, despite being numerous.

4.2. Long-term efficacy of dietary therapy

Once food groups responsible for EoE have been identified, after the reintroduction phase with empirical elimination diets, long-term avoidance of triggering foods has been recommended in order to maintain disease remission. Several small series in adults have demonstrated that full sustained remission is usually present in patients who remain compliant with eliminating known dietary triggers (1–3). In one of the seminal studies on 6-FED in adults, all patients who responded to a 6-FED and adhered to long-term avoidance of identified food triggers maintained full remission (25 patients after 1-yr follow-up, 15 patients after 2-yr follow-up and 4 patients after a 3-yr follow-up period) [83]. Two additional small series on 6-FED in adults each reported 10 similarly compliant patients in remission after 9 months [90] and up to a 2-yr follow-up period [91]. No data in children is available regarding the long-term efficacy of eliminating identified food triggers. Furthermore, all available data refers to 6-FED, so whether long-term compliance might be enhanced with simpler diets (1-, 2- of 4-FED) remains to be demonstrated.

4.3. Long-term adherence

Despite the effectiveness of diet therapy, as already stated, long-term avoidance of food triggers can be difficult, resulting in non-adherence, disease recurrence, and a switch to drug therapy. Long-term adherence is usually low (≤50%) after 1 year (1–3), with the best figures reported being 57% [10]. Factors impacting adherence to diet therapy include treatment effectiveness, social limitations, and diet-related anxiety [10].

4.4. Development of food tolerance over time

As previously mentioned, reintroduction of identified food triggers usually results in clinical and histological relapse [82,83,92]. However, a recent pediatric series has reported 14 patient responders to restrictive diets who remained on full remission, despite reintroduction of all eliminated food allergens [93]. In two large series from the USA, similar results have been published comprising 1.9% [94] and 0.5% [95] of all children undergoing dietary interventions; whereas it represented 9% [85] and 3% [87] of adult responders in recent publications evaluating a 4-FED and the step-up 2-4-6 strategy, respectively. Therefore, there might be a minor subset of EoE patient responders to diet who may develop food-trigger tolerance over time and enter sustained, untreated remission. Beyond food tolerance, sampling error or concomitant effective PPI therapy may also be potential explanations for this intriguing phenomenon.

5. Dupilumab, a new therapeutic option recently arrived in EoE

The U.S. Food and Drug Administration recently approved subcutaneous Dupilumab to treat EoE in adults and pediatric patients 12 years of age and older weighing at least 40 kg. This monoclonal antibody that blocks the shared receptor component for IL-4 and IL-13 (key and central drivers of type 2 inflammation) [96] was already available for the treatment of multiple type 2 inflammatory diseases, including atopic dermatitis, asthma,and chronic rhinosinusitis with nasal polyps.

5.1. Efficacy of dupilumab to induce EoE remission

In a phase 2 study in adults with active EoE, dupilumab 300 mg weekly (qw) improved symptoms, histology and endoscopic features of disease at week 12 compared to placebo: Histologic remission (defined as ≤6 eos/HPF) was observed in 65.2% of patients treated, while 82.6% overall had <15 eos/HPF at the end of therapy [97].

The phase-3 trial involving adults and adolescents, consisted of three parts: Parts A and B were independent 24-week, induction or remission, RCT, and patients who completed Part A or B entered the 28-week extended active treatment Part C. In part A, patients were randomized 1:1 to dupilumab 300 mg qw or matched placebo. In Part B, patients were randomized 1:1:1 to dupilumab 300 mg qw, dupilumab 300 mg q2w, or placebo qw. The primary histologic co-primary endpoint of ≤6 eos/HPF peak count was achieved by 59.5% of patients in part A and 53.3% of patients allocated to dupilumab qw in part B, both being significantly superior to placebo (5.1% and 6.3%, respectively). Also higher proportions of patients achieved <15 eos/hpf under dupilumab treatment (Part A, qw 57.5%, Part B, qw 79.4%, q2w 72.4%, all with $p < 0.001$ compared to placebo) [98].

Although active drug qw and q2w dosages were not different in terms of histologic remission, dupilumab 300 mg qw was the only dose that produced significant benefit over placebo in terms of clinical remission (co-primary endpoint), measured as a 30% reduction in baseline Dysphagia Symptom Questionnaire (DSQ) score. The q2w doses were also not superior to placebo in improving quality of life or disease impact [98].

5.2. Long-term remission of EoE under dupilumab therapy

The effects observed in patient who received Dupilumab qw in Part A were sustained to Week 52 (at the end of Part C): 55.9% maintained histologic remission (≤6 eos/HPF) and 82.4% <15 eos/HPF. Long-term treatment, therefore, did not induce higher rates of remission. As for symptoms, improvements in DSQ for Part A dupilumab-qw-treated patients were sustained to Week 52

Dupilumab was well tolerated: injection-site reactions were the most frequently reported adverse event, with similar incidence across all active drug and placebo groups, none of which were serious or led to treatment discontinuation. Contrarily to previous trials on other dupilumab indications [99], conjunctivitis incidence was low.

6. Conclusion

The recommendation to maintain long-term treatment to prevent recurrence of EoE symptoms and inflammatory activity after successful induction therapy is supported by a number of studies, as well as expert opinion. The effectiveness of available therapies has been shown to be lower when used in maintenance compared to in remission of EoE. However, the drug doses used in the latter are usually lower, and adequate adherence to therapy is not guaranteed. High-quality, long-term prospective studies are needed to definitively establish the benefits of maintenance treatment in EoE.

7. Expert opinion

To date, the majority of studies on pharmacological or dietary therapies for EoE have focused on the evaluation of short-term response, and long-term maintenance therapy has little been evaluated, especially in relation to PPIs and diet. With the exception of a few time-limited clinical trials with STC [46–48], most evidence for maintenance treatment in EoE comes from observational studies, usually retrospective and therefore with potential risks of bias. Available evidence undoubtedly shows that EoE is almost universally chronic in nature [8], characterized by the reappearance of symptoms and esophageal inflammation once any effective kind of therapy is stopped [3,17,95,100]. Similarly, maintenance therapy after successful induction reduces long-term symptoms [101], complications, such as food bolus impaction [45], and the need for esophageal dilation [102]. EoE is still a young disease, first described three decades ago [4], and not until recently has it been considered a relevant problem in gastroenterology, pediatrics, or allergy clinics. Consequently, systematic development of potentially effective therapies for EoE through clinical trials has seen a boost in recent years, mostly for induction therapy. Surprisingly, the first FDA approval of a treatment for EoE consists of a biological therapy. First-line management strategies endorsed currently by evidence-based guidelines [1] and position papers [103] include PPIs (used off-label), topical corticosteroids (also used off-label in many settings) and dietary elimination, with esophageal dilation used as a concomitant therapy to manage fibrostricturing complications [104]. The cost of new therapies, including biologics, will determine somehow their position in the EoE therapeutic algorithm in the future. However, it seems reasonable that EoE patients with other difficult-to-control atopic comorbidities would be best candidates to receive advanced therapy targeting several diseases with a single drug.

Over the past decade, numerous clinical practice guidelines have systematically recommended maintenance treatment with effective anti-inflammatory drug or diet for induction in EoE patients of all ages ('strong recommendation'). This is in spite of a limited, mostly expert opinion-based, level of evidence [1,105,106]. The recommendation is even stronger for those patients who present a more severe form of EoE – with stricture, food impaction or recurrent symptoms off treatment. It is intuitive better to propose maintaining EoE remission with the lowest effective dose of medication, given the potential long-term side effects of the drugs. Consequently, available results have not been able to demonstrate that STC cause a significant risk of adrenal suppression [35], the most common complication being esophageal candidiasis (affecting less than 10% of patients in any study, generally asymptomatic and incidentally detected in surveillance endoscopy). PPIs are also considered safe long-term drugs when used at standard doses [107], but concerns, yet unproven, remain about their prolonged use in children. Dietary long-term maintenance strategy consists of avoiding exclusively the food(s) (usually no more than 2) that have been shown to cause EoE in an individual patient. Under these conditions, long-term nutritional deficiencies seem unlikely, since other permitted foods may supply any nutrient in sufficient amounts [108,109].

In order to define commonly agreed and clinically meaningful end points able to determine treatment efficacy in EoE, a recent consensus of experts proposed a core outcome-set for interventional studies in adult and pediatric patients [110].

According to this, the minimum goal that any therapy aimed at EoE patients should achieve would include: clinical remission, resolution of histopathological changes, endoscopic normalization, and restoration of an adequate health-related quality of life. These goals are applicable to ongoing and future clinical trials for the development of drugs capable of inducing EoE remission, but could also be extended to long-term therapies (although no long-term studies have yet implemented them). In the beginning, the goals of long-term EoE treatment were basically clinical (to prevent symptoms of dysphagia, to prevent food bolus impaction, and to allow adequate nutritional intake) but these were soon shown to be insufficient: Symptoms by themselves are imprecise in predicting the activity of the disease [111,112], and frequently underestimated if inadequate measurement instruments were used [30,113], or if the patient was not questioned about the adoption of adaptation strategies to live with dysphagia [114]. For this reason, normalization of histology is felt by most experts to be the most significant maintenance treatment objective, despite it has not been possible to establish what threshold level of eosinophil density is the most appropriate. Most drugs under study for remission induction now use the <5 or <6 eos/HPF criteria, but clinical experience shows that more conservative targets (i.e., less than <15 eos/HPF) may be acceptable in clinical practice and obtain equivalent results [115]. Future studies should define whether minimal but sustained inflammatory activity is still capable of promoting subepithelial fibrous remodeling and stricture formation in EoE. In this context, the objectives of endoscopic referral take on special relevance.

Ensuring adherence to therapy – the extent to which a person's behaviors correspond with agreed recommendations from their health-care provider – is one of the most challenging aspects in the management of patients with chronic diseases [116], including those with EoE. Once disease activity and symptom remission have been achieved, loss of adherence to any type of therapy has been repeatedly documented in EoE [91,117–119], leading to recurrence of inflammation (with its consequent risk of fibrotic progression) and symptoms. Despite several interventions having been proposed to improve treatment adherence in chronic diseases, the evidence for enhancing medication adherence has generally been weak [120], and interventions in EoE have only just started to be assessed [121].

Rates of adherence to therapy in EoE have been shown to be lower among adolescents and patients with depression [118,122], but improve by the use of medication-taking checklists [118] (which can be effectively monitored by mobile applications) [118]. We do not know if intermittent or occasional pharmacological treatment could be sufficient in maintaining long-term remission in EoE patients, but there is an ongoing clinical trial comparing the results at one year of continuous versus intermittent STC therapy in adult and adolescent patients with this disease (EudraCT 2017–003516-39). For dietary treatment, however, all the evidence seems to indicate that adherence to the diet should be maintained over time, but as already stated, this is not without difficulties. Perception of diet effectiveness, the limitation it imposes on social situations and diet related-anxiety needs to be identified and addressed in each particular patient [10].

Most experts agree that some type of long-term follow-up should be ensured for EoE patients, although it has not yet been possible to define the ideal method or time sequence in which this should be carried out. Clinical practice guidelines also have not made recommendations for the ideal follow-up, which should include, as a minimum, a detailed clinical evaluation, and, in the event of deterioration of symptoms or the appearance of new manifestations, a guaranteed evaluation with endoscopy and biopsies. Similarly, careful follow-up is also seen as essential for all long-term medication approaches, especially in children. The potential inclusion in clinical practice of less invasive methods for esophageal monitoring, such as the esophageal string test [123], the cytosponge [124] or unsedated transnasal endoscopy [125], as well as the availability of novel drugs with predictable and high effectiveness rates currently under development [126], will all contribute to improved maintenance therapy results.

In conclusion, the chronic nature of EoE determines that symptoms, endoscopic features, and histological findings all recur if initially effective anti-inflammatory treatment is stopped. Due to the progressive and stricturing behavior of EoE in most patients, and the evidence that long-term maintenance therapy decreases the risk of esophageal stricture, food bolus impaction, and need for dilation, clinical guidelines recommend maintenance therapy with any proven effective treatment option at the least effective dose. Key unanswered questions include setting best strategies to maintain long-term remission, as well as the criteria to define it. Frequency and causes of loss of adherence and its clinical effects, as well as investigation of the best strategies to ensure it, require further addressing. Finally, routine surveillance methods and frequency still need to be defined.

Acknowledgments

The authors are indebted to Melanie Radcliff for proofreading the English text.

Declaration of interest

A Lucendo has served as a speaker, and/or has received research and/or education funding and/or consulting fees from Adare/Ellodi, Dr. Falk Pharma, Regeneron, and EsoCap. J Molina-Infante has received research and/or education funding from Dr. Falk Pharma. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

One peer reviewer is a consultant for Pulm One, Spoon Guru, ClostraBio, Serpin Pharm, Allakos, Celldex, Nextstone One, Bristol Myers Squibb, Astra Zeneca, Ellodi Pharma, GlaxoSmith Kline, Regeneron/Sanofi, Revolo Biotherapeutics, and Guidepoint; has an equity interest in the first seven listed, and royalties from reslizumab (Teva Pharmaceuticals), PEESSv2 (Mapi Research Trust) and UpToDate; and is an inventor of patents

owned by their institution. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

ORCID

Alfredo J Lucendo http://orcid.org/0000-0003-1183-1072
Javier Molina-Infante http://orcid.org/0000-0003-1204-0571

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•• **A randomized trial that compared a same dose of budesonide given either in an oral viscous slurry or nebulized and then swallowed for 8 weeks, demonstrated the former was more effective in reducing numbers of esophageal eosinophils in patients with EoE, by providing a significantly higher level of esophageal exposure to the drug.**

39. Rubinstein E, Lee JJ, Fried A, et al. Comparison of 2 delivery vehicles for viscous budesonide to treat eosinophilic esophagitis in children. J Pediatr Gastroenterol Nutr. 2014;59(3):317–320.
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42. Rokkas T, Niv Y, Malfertheiner P. A network meta-analysis of randomized controlled trials on the treatment of eosinophilic esophagitis in adults and children. J Clin Gastroenterol. 2021;55(5):400–410.

•• **A network meta-analysis that combined direct and indirect data on the efficiency of drug therapies for EoE evaluated in 17 randomized control trials for EoE and on a total of 1011 patients showed that budesonide 1 mg orodispersible tablet twice daily was the best treatment for EoE, as it was the most effective. This treatment remained the optimal approach in adult patients, whereas fluticasone was the best treatment in pediatric patients.**

43. Helou EF, Simonson J, Arora AS. 3-yr-follow-up of topical corticosteroid treatment for eosinophilic esophagitis in adults. Am J Gastroenterol. 2008;103(9):2194–2199.
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• **A large series of Swiss patients with EoE was evaluated to determine if a lasting remission could be achieved after treatment with topical corticosteroids, and treatment can be stopped once patients have reached this remission. After treatment cessation, the majority of patients experienced a clinical relapse**

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• **First analysis of data from a large, multicenter cohort of patients with EoE in Europe that investigates effectiveness of therapy in a real-world. Topical steroids were found to be the most effective at inducing clinical and histologic remission, but PPIs to be the most frequently prescribed. Treatment approaches vary with institution and presence of fibrosis or strictures.**

54. Tourlamain G, Garcia-Puig R, Gutiérrez-Junquera C, et al. Differences in management of eosinophilic esophagitis in Europe: an assessment of current practice. J Pediatr Gastroenterol Nut. 2020;71(1):83–90.
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- **These systematic review-based expert committee-consensual guidelines were the first ones provided for the management of EoE in children and adults. The available body of knowledge accumulated to that moment was incorporated in the reference document, which also provided recommendation for further research.**

56. Molina-Infante J, Ferrando-Lamana L, Ripoll C, et al., Esophageal eosinophilic infiltration responds to proton pump inhibition in most adults. Clin Gastroenterol Hepatol. 2011;9(2): 110–117.

- **Fifty-three consecutive patients with symptoms of esophageal dysfunction and tissue eosinophilia were defined as EoE or proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE) diagnoses. Baseline cytokine gene expression in PPI- REE was nearly indistinguishable from EoE. PPI therapy significantly downregulated esophageal eotaxin-3/Th2-cytokine gene expression in PPI-REE, similarly to that seen in steroid- responsive EoE.**

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•• **First reasoned questioning of the role of PPIs as a diagnostic instrument in EoE, and proposal to abandon the concept of PPI-responsive esophageal eosinophilia, as it represents a continuum of the same immunological mechanisms that underlie EoE. PPIs are recognized as a therapeutic agent. Due to its safety profile, ease of administration and high response rates (up to 50%), PPI are proposed to be considered a first-line treatment before diet and topical steroids.**

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