Eosinophilic Esophagitis: An Evidence-Based Approach to Therapy

González-Cervera J[1], Lucendo AJ[2]

[1]Department of Allergy, Hospital General de Tomelloso, Tomelloso, Ciudad Real, Spain
[2]Department of Gastroenterology, Hospital General de Tomelloso, Tomelloso, Ciudad Real, Spain

J Investig Allergol Clin Immunol 2016; Vol. 26(1): 8-18
doi: 10.18176/jiaci.0002

Abstract

In recent years, several randomized controlled trials and meta-analyses have evaluated the efficacy of the various therapeutic options available for treating patients with eosinophilic esophagitis, including dietary modifications, proton pump inhibitors, topical corticosteroids, and endoscopic esophageal dilation. Proton pump inhibitors are currently considered the first-line treatment for eosinophilic esophagitis, achieving histological remission and improvement of symptoms in 50.5% and 60.8% of patients, respectively.

The efficacy of topical corticosteroids in eosinophilic esophagitis has been assessed in several trials. Meta-analyses summarizing results indicate that budesonide and fluticasone propionate are significantly superior to placebo, both in decreasing eosinophil densities in the esophageal mucosa and in relieving symptoms. However, owing to differences in drug delivery, viscous budesonide seems to be the best pharmacological therapy for eosinophilic esophagitis.

Results for dietary modifications have been mixed depending on the type of diet prescribed. Thus, while exclusive amino acid–based elemental diets are the most effective in inducing histological remission of eosinophilic esophagitis (90.8%), their severe drawbacks limit their implementation in clinical practice. Allergy testing–based food elimination provides a suboptimal remission rate of 45.5%, although this is lower in adults than in children (32.2% vs 47.9%, respectively). In addition, the various available studies are highly heterogeneous. Empirical 6-food elimination diets were shown to be the best diet-based therapy, with a homogeneous remission rate of 72%. Simpler, more convenient empirical schemes have also been evaluated.

The aim of this review is to provide an evidence-based overview on the efficacy of the options available for treatment of eosinophilic esophagitis along with a practical management algorithm.

Key words: Eosinophilic esophagitis. Diet therapy. Drug therapy. Dilation. Budesonide. Disease management.

Resumen

Varios ensayos clínicos controlados y meta-análisis han evaluado la eficacia de distintas opciones terapéuticas disponibles para la esofagitis eosinofílica (EoE), incluyendo modificaciones dietéticas, inhibidores de la bomba de protones (IBP), esteroides tópicos y dilatación endoscópica. Los IBP constituirían actualmente el tratamiento de primera línea, pues logran remisión histológica y mejoría sintomática en el 50,5% y el 60,8% de los pacientes con EoE, respectivamente.

La eficacia de los esteroides tópicos ha sido evaluada en varios ensayos, cuyos resultados se resumen en posteriores meta-análisis: budesonida y fluticasona resultaron superiores al placebo, disminuyendo la densidad de eosinófilos en la mucosa esofágica y mejorando los síntomas. Sin embargo, debido a su diferente administración, budesonida viscosa podría constituir la mejor terapia.

Igualmente, las modificaciones dietéticas ofrecen resultados variables según la opción empleada. Así, las dietas elementales basadas exclusivamente en aminoácidos resultan las más eficaces para inducir la remisión histológica (90,8%), pero notables inconvenientes limitan su aplicación en la práctica clínica. La eliminación de alimentos dirigida por pruebas de alergia ofrece una tasa de remisión subóptima del 45,5%, menor en adultos que en niños (32,2% frente a 47,9%, respectivamente), con alta heterogeneidad entre los estudios disponibles. Las dietas empíricas de eliminación de seis alimentos constituirían la mejor opción dietética, con una tasa de remisión homogénea del 72%. También han sido evaluados esquemas empíricos más simples y cómodos.

Esta revisión proporciona una visión general basada en evidencias sobre la eficacia de las diferentes opciones de tratamiento para la EoE, y un algoritmo para su manejo práctico.

Palabras clave: Esofagitis eosinofílica. Dietoterapia. Tratamiento farmacológico. Dilatación. Budesonida. Manejo de la enfermedad.

Introduction

Eosinophilic esophagitis (EoE) is a chronic immune-mediated inflammatory disorder defined symptomatically by esophageal dysfunction and histologically by eosinophil-predominant inflammation of the esophagus [1]. First characterized as a distinct clinicopathological disorder 20 years ago, EoE has only recently been recognized as the most prevalent cause of chronic or recurrent esophageal symptoms after gastroesophageal reflux disease. It is also the main cause of dysphagia among children and young adults in Europe and North America [1]. In recent years, it has emerged as an increasingly frequent disorder in other regions such as Central and South America [2-5], Asia [6-8], and North Africa [9,10]. As a result, EoE currently represents a growing chronic health problem that, owing to its prevalence, is becoming a significant burden for a number of health care systems. For example, in the United States, care of patients with EoE is now estimated to cost up to $1.4 billion annually [11].

Since its initial descriptions in the early 1990s, EoE has been recognized as a specific form of food allergy [12]. In the decade after its discovery, a handful of studies developed mainly in pediatric patients described the high efficacy of exclusive feeding with amino acid–based elemental diets to achieve disease remission [13-15]. At the same time, practitioners were using an expanding range of options for treating EoE, from endoscopic dilations aimed at resolving esophageal strictures through physical enlargement of the esophagus to drug regimens based on topical corticosteroids, antiallergy agents, and even monoclonal antibodies [16]. In recent years, well-designed clinical research, including randomized controlled trials (RCTs) and quasi-experimental prospective studies, has assessed the efficacy of the therapeutic options available for achieving and maintaining disease remission in patients with EoE. Recently, this growing body of evidence has also been summarized in systematic reviews and meta-analyses to provide clinicians with better quality data for making decisions concerning the complex management of this disorder.

The aims of this review are to provide an evidence-based overview of the efficacy of the therapeutic options available for treating children and adults with EoE, as well as to discuss their ease of use, advantages, and limitations. Finally, guidance for successful implementation of these options in clinical practice will be given.

Dietary Therapy in EoE

The Origins: Elemental Diets

The first evidence on the efficacy of dietary interventions in inducing remission of EoE was published in 1995 by Kelly et al [12], who exclusively used a nonantigenic amino acid–based formula to feed a series of 10 children with severe EoE that had initially been attributed to gastroesophageal reflux disease and was refractory to other therapies. After a minimum of 6 weeks, the disease had completely resolved in 8 children, with the remaining 2 showing symptomatic improvement and a significant reduction in the eosinophilic infiltrate. This result demonstrated that EoE was primarily an immune reaction to food proteins. The high efficacy of elemental formulas has been confirmed repeatedly in subsequent reports in both children and adolescents with EoE [13-15] and more recently in adults [17]. Despite a lack of RCTs, a meta-analysis has shown that the overall efficacy of elemental diets in inducing histological remission of EoE (ie, a reduction in peak eosinophil counts to <15 per HPF) is 90.8% (95%CI, 84.7%-95.5%) [18].

In terms of inducing histological remission of EoE, elemental diets have been shown to outperform not only all other dietary modification strategies, but also treatment with topical corticosteroids [19]. However, they are not recommended as first-line therapy for EoE. Indeed, their use in clinical practice is very limited owing to several disadvantages that have a serious impact on adherence to treatment. From the very beginning, the palatability of elemental formulas was recognized as a serious limitation, since administration is via nasogastric tube in most children, with only 20% of pediatric patients being able to ingest the formula orally [14]. Subsequent studies showed that up to one-third of adult patients recruited for a 4-week trial were unable to adhere to therapy [17].

Such a restrictive and monotonous diet also has an enormous impact on a patient's psychological well-being and social life, aggravating the feeling of being different from their families and peers that children with EoE usually express [20]. In adults, this type of therapy can exacerbate the impact of eating/dietary and social problems through which EoE commonly diminishes a patient's health-related quality of life [21,22]. Furthermore, the high cost of elemental formulas means that they are not universally covered by health insurance. For example, providing a patient with a daily intake of 2000 kcal exclusively with elemental diets costs €56 per day in Spain. Thus, because they are impractical to implement over long periods, elemental diets do not represent a proper nutritional alternative for a chronic disease like EoE. The only real utility of this diet in clinical practice is restricted to small children who are not yet on solid foods if symptoms and inflammation persist and no narrowing is observed, and especially if a rapid clinical improvement is required. It could be also considered for patients in whom a 6-food elemental diet has failed to identify the trigger food(s), when concerns about unusual food antigens come into play, and when the dietary restrictions involved in an exclusively elemental diet can be tolerated. However, these circumstances require further research.

Allergists Step up to the Plate: Allergy Testing–Driven Food Elimination

Repeated demonstrations of EoE as a specific form of food allergy that went into remission after avoidance of exposure to food proteins led allergists to try to identify the food(s) responsible for the disease. The first attempts were based on examination of the clinical histories of the affected patients, which was unsuccessful, because patients do not generally associate the onset of symptoms with consumption of specific foods. Consequently, researchers tried using actual allergy testing methods, including both skin prick tests and atopy patch tests. This method was thought to be capable of identifying the

specific food(s) to be avoided while providing patients with convenience, feasibility, and improved quality of life, as they would only have to eliminate certain foods to achieve results similar to those obtained with elemental diets. Unfortunately, these goals could not be achieved.

In 2002, a combination of skin prick tests and atopy patch tests was used for the first time to identify the food(s) responsible for EoE in a series of children from Philadelphia (Pennsylvania, USA). Exclusion of an average of 5 foods from each child's diet (those that produced positive skin test results) led to clinical and histological remission in 49% of treated patients [23]. These initial results were updated by the same research group after a decade of experience, with an overall efficacy of 53% [24]. Notably, the sensitivities and specificities of allergy skin testing varied greatly, with less than 10% of all positive results concordant in both skin prick tests and atopy patch tests. In addition, these tests repeatedly showed an extremely low sensitivity for cow's milk, the main trigger food for EoE, as discussed below. The strategy of empirically eliminating cow's milk from the diet while also avoiding foods that produced positive skin allergy test results led to remission rates of up to 77% [24]. However, this approach is not strictly based on skin allergy testing alone.

It is interesting to note that although the Consensus Guidelines recognized early on that the diagnostic accuracy of skin allergy testing was insufficient for designing effective diets for EoE patients [1], many researchers continued to use the strategy of excluding food that had given positive skin test results in an attempt to induce remission of EoE. Their inconsistent and modest results were recently summarized in a systematic review [18], which demonstrated that the remission rate achieved with this strategy was only 45.5% (95%CI, 35.4%-55.7%), with broad heterogeneity in the results, indicating low reproducibility. Moreover, these results were significantly lower for adults than for children (32.2% vs 47.9%).

Compared with controls, patients with EoE are usually sensitized to several different foods and aeroallergens, as demonstrated not only by skin allergy test results, but also by higher values of serum food-specific IgE. After repeated studies documenting the very limited utility of serum food-specific IgE in the management of EoE patients [25-27], the strategy of measuring specific IgE against single allergen molecules by means of microarray assay–based component-resolved diagnosis (CRD) was also recently assessed for its potential to guide specific dietary management of EoE [28,29]. However, a prospective study failed to demonstrate the efficacy of CRD-based dietary treatment in EoE patients.

In parallel with the repeatedly documented limitations of IgE-based allergy testing for controlling EoE, there is a growing body of evidence against the involvement of IgE-mediated reactions in the pathogenesis of the disease [30]. Moreover, EoE is increasingly recognized as a disease that is basically restricted to the esophagus, with very limited systemic expression [31]. Thus, serum IgE levels do not necessarily correlate with the clinical or histopathological activity of the disease and have repeatedly shown very limited sensitivity and specificity (around 50%) for identifying the foods responsible for EoE [25,26,32]. Exposure to such trigger foods rarely causes anaphylaxis [33]. Furthermore, although local synthesis of IgE has been demonstrated in the esophageal mucosa of children with EoE regardless of whether they display other forms of atopy [34], this IgE does not seem to mediate immediate immune reactions. In addition, mast cells, a cell type that is abundant in the inflammatory infiltrate of EoE patients and that is usually activated by IgE, show no significant differences in density or activity between patients with atopic and nonatopic EoE [35]. Blocking IgE with monoclonal antibodies (omalizumab) has repeatedly been found to be ineffective in improving EoE in children and adults, according to observational studies and a recent RCT [36-38]. In fact, EoE has recently been recognized as an IgG4-associated disorder rather than an IgE-mediated disease [38] after dense infiltration by IgG4-positive plasma cells was observed around the vessels of the lamina propria of adult EoE patients.

Empiric Elimination of Common Dietary Antigens: Currently the Best Approach

(*a*) The 6-food elimination diet. Owing to the many disadvantages of elemental diets and the low diagnostic accuracy of skin allergy testing in identifying EoE trigger foods, researchers turned to the alternative of empirically removing from the patient's diet the 6 types of foods most often associated with food allergies in children (milk protein, wheat, eggs, soy, peanuts/tree nuts, and fish/seafood) [15]. This initial study showed that after a 6-week period, this so-called 6-food elimination diet (SFED) led to disease resolution (defined as the absence of symptoms and fewer than 10 eosinophils/HPF in esophageal biopsies) in 26 out of 35 patients (74%), as well as a partial remission (<20 eosinophils/HPF) in a further 3 patients. Subsequent prospective studies involving adult patients reproduced these results [26,32]. Moreover, a meta-analysis of 7 studies demonstrated that the overall effectiveness of an empiric SFED in inducing remission of eosinophilic infiltration in EoE to levels below the diagnostic threshold was 72% (95%CI, 66%-78%), with high concordance in the remission rate, expressed as a heterogeneity value of 0% (I^2 statistic). This lack of variability compared with that observed with food elimination based on skin test results (I^2 of 75.1%), as well as its much higher adherence rates in comparison with elemental diets, makes empiric elimination diets the most recommendable treatment approach in the initial dietary management of EoE. However, the removal of 6 types of foods to achieve remission of EoE must only be taken as a first step in the treatment of patients with the disease, to be followed in all cases by progressive reintroduction of food(s) to identify the specific food(s) responsible for EoE while providing patients with a more varied diet.

(*b*) A more convenient 4-food elimination diet. After sequential reintroduction of food(s), only 1 or 2 foods are identified as responsible for EoE in 65% to 85% of all EoE patients, irrespective of age. Thus, restricting a large number of foods and then undertaking sequential reintroduction may be unnecessary in many cases. This approach has the advantage of being better accepted by patients, as the diet is less restrictive, while also shortening the time needed to identify the food(s) responsible for EoE, which in turn means fewer endoscopic procedures. In a prospective multicenter study carried out in

Spain, the empiric elimination of the 4 foods most frequently associated with triggering and maintaining EoE (wheat, milk, eggs, and legumes including soy) led to disease remission in 28 out of 54 adult patients (54%) [39], with a significant proportion of nonresponders to the 4-food elimination diet (31%) achieving remission upon following an empiric 6-food elimination diet. The final results indicated an overall efficacy of 72%, similar to that observed with a 6-food elimination diet. Even better results have been reported in children taking part in a second prospective multicenter study carried out in the USA, with remission achieved in 39 of 55 children (71%) following a 4-food elimination diet [40].

(*c*) Empiric elimination of cow's milk. Cow's milk is the food most frequently associated with EoE in both children [41,42] and adults [26,32,39]: it is implicated in the origin of the disease in up to half of all patients. The restriction of cow's milk exclusively in 17 children with EoE was shown to achieve a remission rate of 65% in one retrospective report [43], an unexpectedly high efficacy that was perhaps influenced by the patient selection criteria. In fact, according to a recent meta-analysis, up to 2.7% of patients with a previous IgE-mediated food allergy who underwent desensitization later developed EoE [44]. In a similar vein, a recent comparative study showed that eliminating milk from the diet normalized esophageal histology in 64% of EoE patients [45], although these results are questionable, since all the study participants also received concomitant treatment with proton pump inhibitors (PPIs), a strategy that by itself is capable of resolving esophageal inflammation in half of all EoE patients [46].

Sequential Reintroduction of a Single Food to Identify Specific Triggers of EoE

The goal of the aforementioned dietary treatment strategies is to induce remission of EoE as a reference point for subsequent identification of potential food triggers. Consuming a previously excluded food after obtaining histological remission of EoE is equivalent to a food challenge test, which is the gold standard for the diagnosis of food allergies. The repeatedly documented dissociation between clinical symptoms and histology in EoE [47] implies that the absence of symptoms is not equivalent to disease remission in all cases. Disease monitoring using repeated endoscopies and systematically performed mucosal esophageal biopsies is thus considered necessary to identify with certainty whether a given food is triggering EoE and should be removed from the diet or whether it is well tolerated and can be consumed regularly. The acceptance of this strategy by patients largely depends on whether sedation is provided during endoscopy and on the commitment to performing them in well-defined time frames after reintroduction of the food. At the end of the reintroduction period, only the food(s) responsible for triggering and maintaining the disease in each individual patient should be avoided indefinitely [48].

In addition to their therapeutic role, dietary interventions in EoE patients should be considered diagnostic methods for identifying specific food triggers. As such, their implementation in the medium and long terms should be guaranteed. Dietary treatment should thus be understood as a succession of 3 main phases, throughout which the targets vary depending on the diet followed by the individual patient [49], as follows:

(*a*) Remission phase: During the minimum 6 weeks that this phase should take, the maximum number of foods is simultaneously removed from the patient's diet. Optimal adherence to the very restrictive diet during this phase is necessary, because if the patient does not respond, the opportunity to follow a drug-free treatment will be lost. Supplementation with elemental formulas may occasionally be needed to ensure an adequate supply of basic nutrients, especially in younger patients [26]. After this period, endoscopy with biopsy, preferably with the patient under sedation, must be scheduled to monitor disease remission.

(*b*) Food reintroduction phase: In patients who achieve histological remission, reintroduction of a single food (ie, a series of food challenge tests) will be undertaken to identify the specific food(s) triggering EoE in a given patient while enabling an increasingly varied diet. In this phase, previously excluded foods are progressively reintroduced individually. It is important that patients be advised of the convenience of regular daily intake of the reintroduced food rather than occasional consumption. There seems to be no need for a washout period prior to the reintroduction of a new food after the demonstration of a recurrence of esophageal inflammation upon reintroduction of the food. Endoscopic assessment with biopsies 6 weeks after the reintroduction of each individual food should also be scheduled.

(*c*) Maintenance phase: Once the food(s) responsible for EoE in each individual patient has been identified, long-term avoidance should be recommended in order to maintain disease remission. The success of this phase largely depends on the patient's ability to effectively substitute the offending food(s) with other permitted alternatives.

Data on the sustained efficacy of avoiding the consumption of foods responsible for EoE has been provided by 2 studies conducted in adults [26,50] and 1 in children [41]: all patients who managed to avoid the trigger food(s) remained asymptomatic, with histological remission in esophageal biopsies, for a period of up to 3 and 5 years, respectively, making drug treatment unnecessary.

Drug Therapy

Proton Pump Inhibitors: A First-Line Therapy That Goes Beyond Inhibiting Acid Secretion

Since 2005, several case series [51-54] and a large prospective series [55] have repeatedly reported that patients with clinical, endoscopic, and histological features of EoE were able to achieve high rates of complete remission after an 8-week course of PPIs. Two RCTs comparing esomeprazole with aerosolized fluticasone propionate [56,57] showed that PPIs achieved a histological response in 33% of EoE patients, despite normal 24-hour pH monitoring. These observations gave rise to a provisional category of the disease, namely, *PPI-responsive esophageal eosinophilia* (PPI-REE), which

refers to patients who initially appear to have clinical EoE, but who achieve complete remission after PPI therapy. This novel phenotype was recognized in the updated 2011 consensus recommendations on EoE [1] and has been endorsed in all subsequent guidelines [58,59]. However, cumulative evidence to date largely supports the idea that PPI-REE constitutes a subphenotype of EoE rather than a distinct disease entity [60], especially since PPI-REE and EoE remain indistinguishable based not only on clinical, endoscopic [61,62], and histological findings [63], but also on pH monitoring [55], the measurement of biological tissue markers [64-66] including cytokines related to eosinophilic inflammation, and esophageal gene transcripts. In addition, monotherapy with PPIs completely reverses cytokine and gene transcript levels in patients with PPI-REE, much in the same way as topical corticosteroids in EoE [67]. Finally, an effective response to dietary therapy, topical corticosteroids, and PPIs has been found in these patients [68,69]. Therefore, PPI-REE patients have been reclassified as EoE patients who respond to PPI therapy, and PPIs are now considered a therapeutic option for effective management of EoE in a high proportion of patients [70].

A recent systematic review with a meta-analysis summarizing the results of 33 studies comprising 619 patients revealed that PPIs enabled histological remission in 50.5% (95%CI, 42.2%-58.7%) of patients with suspected EoE, while 60.8% (95%CI, 48.38%-72.2%) of patients reported relief from symptoms [46]. No significant differences due to patient age, study design, or type of PPI assessed were observed. A trend towards increased efficacy was noted when PPIs were administered twice daily as opposed to once daily.

The long-term efficacy of PPIs in maintaining remission in PPI-REE has been assessed in a retrospective multicenter study in adult patients [71]. Most patients (73%) maintained histological remission 1 year after the dosage was tapered to the minimum effective dose. Patients who experienced a recrudescence of inflammation while on lower PPI doses regained histological remission after dose escalation, suggesting that twice-daily doses are needed in some patients. Interestingly, 90% of the relapsers were rapid CYP2C19 metabolizers. The sustained efficacy of PPIs in children has been evaluated in a recent prospective study, with most patients (11/14, 78.6%) remaining in clinicopathological remission at 1-year follow up while on maintenance PPI therapy [72].

Topical Corticosteroids: A Reference Standard Revisited

After they were shown to have the same effect as prednisone in an RCT [73], swallowed topical corticosteroids have now replaced systemic corticosteroids for the treatment of EoE, especially since the latter, which present no advantages in terms of symptom resolution, relapse rates, or time to relapse, have significantly more severe adverse effects. The use of systemic corticosteroids has thus been restricted to emergency situations with severe dysphagia or significant weight loss.

In the last year, 3 meta-analyses have summarized the evidence from 7 RCTs on the efficacy of topical corticosteroids in inducing remission of EoE [74-76]. Both budesonide and fluticasone propionate were shown to be significantly superior to placebo in decreasing eosinophil density in the esophageal mucosa [76,77]. In parallel, symptom relief was also significantly more frequent in patients who received corticosteroids than in the placebo group (OR, 3.12; 95%CI, 1.44-6.75) [74]. Moreover, topical corticosteroids were more efficacious in reducing peak eosinophil counts in adults than in children [76], although this difference was not statistically significant. A trend towards the superiority of viscous budesonide over aerosolized fluticasone was also observed [76].

Notably, topical corticosteroids were not found to be superior to PPIs in terms of histological remission (OR, 0.45; 95%CI, 0.15-1.40) or clinical improvement (OR, 2.67; 95%CI, 0.52-13.66) in 2 of the meta-analyses [74,75], although these results should be viewed with caution owing to the limited number of original studies included.

The results of the meta-analyses discussed above showed significant heterogeneity in the efficacy of topical corticosteroids, most likely owing to the various doses of drug used, the different drug administration routes, and the different populations included in each RCT. In fact, the importance of the vehicle used to release a topical corticosteroid into the esophagus was highlighted in an RCT that compared 2 formulations of budesonide (oral viscous and nebulized) given at the same doses [77]. Oral viscous budesonide provided a higher level of esophageal exposure owing to a more prolonged contact between the mucosa and the medication, as measured with the aid of scintigraphy, resulting in significantly higher esophageal eosinophil counts and endoscopic findings. In this sense, budesonide formulations designed to achieve and remain in contact with the esophageal mucosa have proven more effective than previous drug formulations. In this context, a recent RCT investigated the efficacy and safety of 2 different budesonide formulations (effervescent tablets for orodispersible use and viscous suspension) with 2 different daily dosages for short-term treatment of EoE in adults [78]. The results of the per protocol analysis showed an efficacy of 100% in each group, even with different doses, after only 2 weeks of treatment.

The superiority of viscous budesonide was likewise demonstrated in a recent network meta-analysis, which found it to be the most effective short term pharmacological therapy for EoE of all the available drug treatments assayed [79].

In contrast, evidence of the ability of topical corticosteroids to maintain remission of EoE over the long term is scant, with only 1 RCT finding low-dose budesonide to be more effective than placebo in maintaining EoE in histological and clinical remission [80].

The main side effect of topical corticosteroids reported in the literature is the development of esophageal *Candida* infection, which is present in around 10% of treated patients [75,78], mostly as asymptomatic findings identified in follow-up endoscopies. Isolated cases of herpes simplex virus–induced esophagitis have been reported in patients with EoE, irrespective of whether they were taking topical corticosteroids [81,82]; therefore, this cannot be considered a true adverse effect of corticosteroid therapy.

As for the effect of topical corticosteroids on adrenal suppression in EoE patients, the low number of long-term studies precludes any definitive conclusions concerning the

possible effects of these drugs on the bone mineral density or growth rates of treated patients. However, the long-term safety of topically administered corticosteroids for treating bronchial asthma in children was established in a systematic review [83] and there is no reason to believe that the results for EoE should be any different. Thus, despite the fact that a recent retrospective study involving patients treated with oral viscous budesonide for more than 3 months found suboptimal 1-μg ACTH-stimulated cortisol values in 6 out of 14 patients [84], no adrenal suppression was documented in other studies monitoring morning cortisol serum levels [85-87].

Monoclonal Antibodies: A Disappointing Sequence

After demonstrating the inefficacy of the anti–tumor necrosis factor α agent infliximab in a small open-label series of EoE patients [88], researchers decided to study the effects of anti–interleukin (IL) 5 antibodies in the treatment of EoE. Mepolizumab was tested in an RCT involving children [89] and in an RCT involving adults [90], while reslizumab was evaluated in children only [91]. Overall, there were no significant differences between the active and placebo groups in terms of symptom relief, and histological remission of EoE was not achieved with any of the anti–IL-5 drugs studied [74]. It would thus seem that these drugs do not constitute a valid treatment option for EoE.

Similarly, after showing no benefits in observational research in adults and children [36,37], the anti-IgE agent omalizumab exhibited no beneficial effects in an RCT involving adult patients with EoE [38].

More recently, researchers published the first RCT evaluating the efficacy of the anti–IL-13 monoclonal antibody QAX576 in 48 adult patients with EoE [92]. The drug failed to achieve the primary endpoint of a >75% reduction in the eosinophilic infiltrate compared to a placebo and did not significantly improve symptoms. However, QAX576 induced relevant normalization of changes in EoE-associated gene expression, including those in eotaxin-3, periostin, and mast cell/epithelial barrier permeability–related genes. The effect persisted for 6 months after treatment.

Endoscopic Dilation

The chronic inflammatory phenomena that characterize EoE cause subepithelial collagen deposition and fibrous remodeling in both children [93,94] and adults [95,96]. Mechanical dilation by means of through-the-scope hydropneumatic balloons or Savary bougies has thus constituted a treatment option for EoE since its earliest descriptions. The goals of mechanical dilation are 2-fold: first, to relieve dysphagia, and, second, to achieve an esophageal caliber that allows for proper swallowing of solid foods. The minimum standard measurement is at least 13 mm, but most authors recommend a final caliber of 15-18 mm [97,98]. Since esophageal dilation has no effect on the underlying inflammatory process, it should not be used as the sole therapy in treating EoE patients.

According to a recent meta-analysis [99], some degree of symptomatic improvement resulting from dilation occurs in 75% of patients, at least in the short term. Dilation should thus be offered to symptomatic EoE patients with significant esophageal strictures or persistence of symptoms after adequate control of eosinophilic inflammation. According to a recent RCT [100], in patients with no severe strictures (an esophageal diameter <7 mm) at diagnosis of EoE, esophageal dilation did not result in additional improvements in the dysphagia score when compared with treatment with either PPIs or fluticasone alone. Interestingly, one cost analysis study found that dilation was generally less economical than treatment with swallowed aerosolized corticosteroids in EoE patients [101].

The long-term efficacy of esophageal dilation has been assessed in at least 1 retrospective series, in which 13 patients treated with both esophageal dilation and daily antacids were evaluated over a mean follow-up period of 13.6 years. Patients initially underwent an average of 3.2 dilations during the first year; after that, regular dilations were needed about every 2 years, depending on symptom recurrence, to maintain symptom remission [102].

Esophageal dilation has been associated with risks in EoE patients. Reports before 2008 warned of an increased risk of deep mucosal lacerations, hospital admissions for chest pain, and even esophageal perforation [103-106]. More recently, however, several large retrospective series [97,98,107] and 2 systematic reviews [99,108] have demonstrated that esophageal perforation after dilation in EoE occurred in less than 1% of cases, which is similar to the risk involved in dilating esophageal strictures caused by other etiologies.

Therapeutic Algorithm in EoE: Just Applying the Evidence

The goals of EoE treatment should include resolution of symptoms, achieving and maintaining remission of the eosinophilic mucosal inflammation to prevent fibrotic esophageal complications, avoidance of iatrogenic drug effects and nutritional deficiencies, and maintaining adequate quality of life.

Based on the information available from high-quality research on the treatment and prognosis of the disease, we propose a therapeutic algorithm for effective management of EoE in both children and adults (Figure). Our algorithm is based on several simple principles, as follows:

(*a*) Owing to their safety [109], ease, low cost, and moderate efficacy, PPIs should be considered first-line therapy for patients with EoE. Patients who achieve clinicopathological remission with PPIs can thus avoid or delay further dietary restrictions and chronic corticosteroid therapy.

(*b*) Since various dietary and pharmacological options have proven effective in achieving remission of EoE, simultaneously combining different treatment modalities in the same patient is not justified. Thus, it is unnecessary to impose dietary restrictions in all cases, as they generally add no benefit to effective therapy with swallowed topical corticosteroids or PPIs, but have a negative impact on a patient's quality of life. In fact, when several therapeutic modalities are applied simultaneously, it makes it more difficult to discern which is the most effective in controlling the disease and should therefore be maintained in the long term.

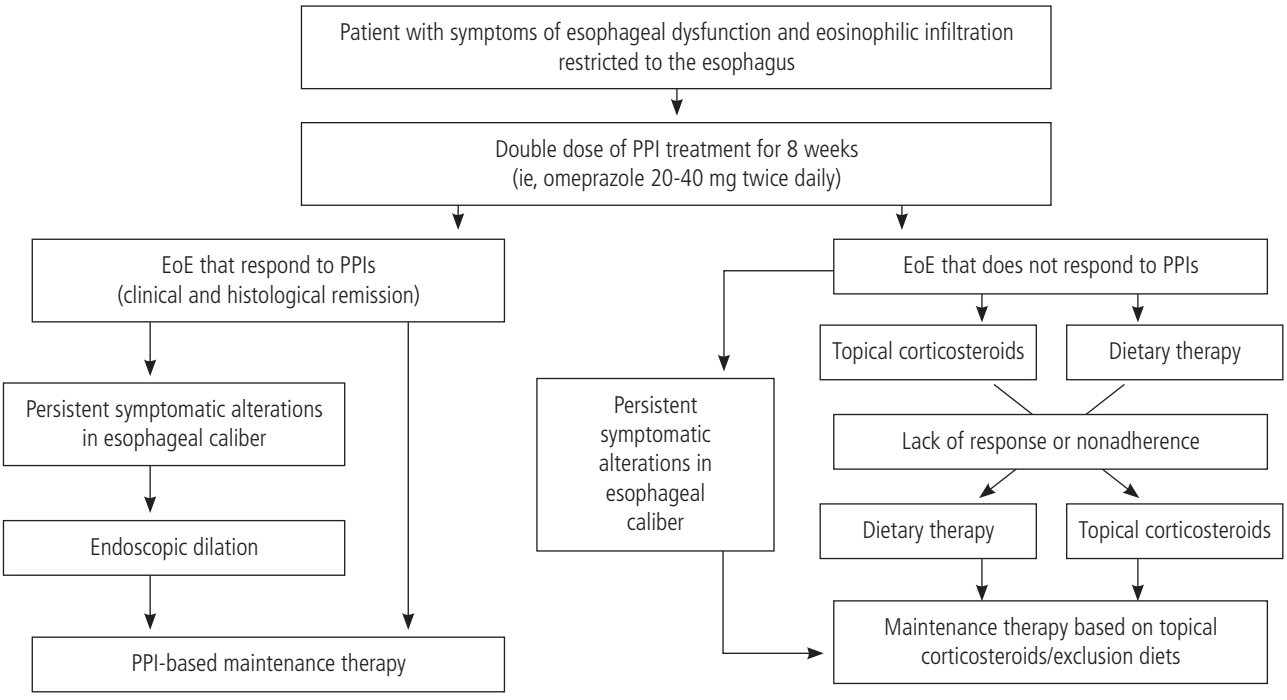

Figure. Evidence-based stepwise treatment algorithm proposed for eosinophilic esophagitis. PPI indicates proton pump inhibitor.

(*c*) The well-documented clinical-histological dissociation in EoE precludes predicting the absence of active eosinophilic inflammation in a patient with no obvious symptoms. Therefore, the response to each therapeutic option should be monitored with endoscopies and biopsies until less invasive surrogate markers of activity are identified.

(*d*) If therapy with PPIs fails, the choice between swallowed topical corticosteroid treatment and dietary restrictions should be offered to the patient. The decision should be based on the patient's (or his/her family's) own preferences, intellectual level, and ability to manage dietary restrictions and substitutions, as well as the severity of symptoms, the practitioner's professional skills, and local availability of resources.

(*e*) Since EoE is a chronic disease, the patient's needs may evolve over time. This means that the preferred therapeutic option may need to be modified to satisfy a given patient's characteristics at different moments.

Conclusion

Because PPIs, topical corticosteroids, and dietary therapies (especially those based on empirical approaches) have all proven to be effective treatment options for achieving and maintaining disease remission, they should be offered to both children and adults with EoE. Current evidence from systematic reviews of RCTs allows for an evidence-based therapeutic approach to EoE, as well as a flexible algorithm that should be modified according to patient needs and preferences, health care facilities and resources, and the evolving circumstances of a chronic disease.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Funding

The authors declare that no funding was received for the present study.

References

1. Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, Burks AW, Chehade M, Collins MH, Dellon ES, Dohil R, Falk GW, Gonsalves N, Gupta SK, Katzka DA, Lucendo AJ, Markowitz JE, Noel RJ, Odze RD, Putnam PE, Richter JE, Romero Y, Ruchelli E, Sampson HA, Schoepfer A, Shaheen NJ, Sicherer SH, Spechler S, Spergel JM, Straumann A, Wershil BK, Rothenberg ME, Aceves SS. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol. 2011;128:3-20.
2. Rezende ER, Barros CP, Ynoue LH, Santos AT, Pinto RM, Segundo GR. Clinical characteristics and sensitivity to food and inhalants among children with eosinophilic esophagitis. BMC Res Notes. 2014;7:47.
3. Pinheiro MI, de Goes Cavalcanti LP, Honorio RS, de Alencar Moreno LH, Fortes MC, da Silva CA. Eosinophilic esophagitis in brazilian pediatric patients. Clin Med Insights Pediatr. 2013;7:41-8.
4. Cruz-Patino E, Ruiz J, I, Meixueiro DA, Grube PP, Roesch-Dietlen F, Remes-Troche JM. Eosinophilic esophagitis prevalence in an adult population undergoing upper endoscopy in southeastern Mexico. Dis Esophagus. 2015;28:524-9.

5. Rodríguez H, Cuestas G, Sasson L. Eosinophilic esophagitis associated with laryngeal papillomatosis in a child. Acta Otorrinolaringol Esp. 2014;65:383-4.
6. Tomomatsu Y, Yoshino J, Inui K, Wakabayashi T, Kobayashi T, Miyoshi H, Kosaka T, Yamamoto S, Torii Y. Clinical features of eosinophilic esophagitis: ten Japanese cases. Dig Endosc. 2013;25:117-24.
7. Shimura S, Ishimura N, Tanimura T, Yuki T, Miyake T, Kushiyama Y, Sato S, Fujishiro H, Ishihara S, Komatsu T, Kaneto E, Izumi A, Ishikawa N, Maruyama R, Kinoshita Y. Reliability of symptoms and endoscopic findings for diagnosis of esophageal eosinophilia in a Japanese population. Digestion. 2014;90:49-57.
8. Ma X, Xu Q, Zheng Y, Zhao Y, Lu J, Wang R, Li Z, Zou D, He J. Prevalence of Esophageal Eosinophilia and Eosinophilic Esophagitis in Adults: A Population-Based Endoscopic Study in Shanghai, China. Dig Dis Sci. 2015;60:1716-23.
9. Saadah OI, Aburiziza AJ, bu Shakra RI. Eosinophilic esophagitis in children from Western saudi arabia: relative frequency, clinical, pathological, endoscopic, and immunological study. Gastroenterol Res Pract. 2012;2012:328253.
10. Hunter SS, Helmy DO, Zayedl NA, El-Tayeb TM, El-Serafy MA. Eosinophilic esophagitis in Egyptian adult patients presenting with upper gastrointestinal symptoms. Open J Gastroenterol. 2014;4:88-95.
11. Jensen ET, Kappelman MD, Martin CF, Dellon ES. Health-Care Utilization, Costs, and the Burden of Disease Related to Eosinophilic Esophagitis in the United States. Am J Gastroenterol. 2015;110:626-32.
12. Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. Gastroenterology. 1995;109:1503-12.
13. Markowitz JE, Spergel JM, Ruchelli E, Liacouras CA. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. Am J Gastroenterol. 2003;98:777-82.
14. Liacouras CA, Spergel JM, Ruchelli E, Verma R, Mascarenhas M, Semeao E, Flick J, Kelly J, Brown-Whitehorn T, Mamula P, Markowitz JE. Eosinophilic esophagitis: a 10-year experience in 381 children. Clin Gastroenterol Hepatol. 2005;3:1198-206.
15. Kagalwalla AF, Sentongo TA, Ritz S, Hess T, Nelson SP, Emerick KM, Melin-Aldana H, Li BU. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2006;4:1097-102.
16. Attwood S, Sabri S. Historical aspects of eosinophilic esophagitis: from case reports to clinical trials. Dig Dis. 2014;32:34-9.
17. Peterson KA, Byrne KR, Vinson LA, Ying J, Boynton KK, Fang JC, Gleich GJ, Adler DG, Clayton F. Elemental diet induces histologic response in adult eosinophilic esophagitis. Am J Gastroenterol. 2013;108:759-66.
18. Arias A, González-Cervera J, Tenias JM, Lucendo AJ. Efficacy of dietary interventions in inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. Gastroenterology. 2014;146:1639-48.
19. Molina-Infante J, Lucendo AJ. Update on topical steroid therapy for eosinophilic esophagitis. Gastroenterol Hepatol. 2015;38:388-97.
20. Franciosi JP, Hommel KA, DeBrosse CW, Greenberg AB, Greenler AJ, Abonia JP, Rothenberg ME, Varni JW. Quality of life in paediatric eosinophilic oesophagitis: what is important to patients? Child Care Health Dev. 2012;38:477-83.
21. Taft TH, Kern E, Kwiatek MA, Hirano I, Gonsalves N, Keefer L. The adult eosinophilic oesophagitis quality of life questionnaire: a new measure of health-related quality of life. Aliment Pharmacol Ther. 2011;34:790-8.
22. Lucendo AJ, Sánchez-Cazalilla M, Molina-Infante J, Pérez-Martínez I, Tenías JM, Barrio J, Nantes Ó, Ciriza-de-los-Ríos C, Perelló A, Arias Á. Transcultural adaptation and validation of the "Adult Eosinophilic Esophagitis Quality of Life Questionnaire" into Spanish. Rev Esp Enf Dig. 2014;106:386-94.
23. Spergel JM, Beausoleil JL, Mascarenhas M, Liacouras CA. The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. J Allergy Clin Immunol. 2002;109:363-8.
24. Spergel JM, Brown-Whitehorn TF, Cianferoni A, Shuker M, Wang ML, Verma R, Liacouras CA. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. J Allergy Clin Immunol. 2012;130:461-7.
25. Rodríguez-Sánchez J, Gómez Torrijos E, López Viedma B, de la Santa Belda E, Martín Dávila F, García Rodríguez C, Feo Brito F, Olmedo Camacho J, Reales Figueroa P, Molina-Infante J. Efficacy of IgE-targeted vs empiric six-food elimination diets for adult eosinophilic oesophagitis. Allergy. 2014;69:936-42.
26. Lucendo AJ, Arias A, Gonzalez-Cervera J, Yague-Compadre JL, Guagnozzi D, Angueira T, Jiménez-Contreras S, González-Castillo S, Rodríguez-Domíngez B, De Rezende LC, Tenias JM. Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. J Allergy Clin Immunol. 2013;131:797-804.
27. Lucendo AJ, Arias A, Tenías JM, Rodriguez-Sanchez J, Gomez-Torrijos E, Feo-Brito F, Molina-Infante J. Serum IgE-targeted elimination diets for treating eosinophilic esophagitis: things are not what they seem. Allergy. 2014;69:1567-8.
28. Armentia A, Martín S, Barrio J, Martín B, García JC, Vega JM, Sánchez A, Fernández P, Corell A. Value of microarray allergen assay in the management of eosinophilic oesophagitis. Allergol Immunopathol (Madr). 2015;43:73-80.
29. van Rhijn BD, Vlieg-Boerstra BJ, Versteeg SA, Akkerdaas JH, van Ree R, Terreehorst I, Sprikkelman AB, Verheij J, Smout AJ, Bredenoord AJ. Evaluation of allergen-microarray-guided dietary intervention as treatment of eosinophilic esophagitis. J Allergy Clin Immunol. 2015;136(4):1095-7.e3. doi: 10.1016/j.jaci.2015.02.038.
30. Simon D, Cianferoni A, Spergel JM, Aceves S, Holbreich M, Venter C, Rothenberg ME, Terreehorst I, Muraro A, Lucendo AJ, Schoepfer A, Straumann A, Simon HU. Eosinophilic esophagitis is characterized by a non-IgE-mediated food hypersensitivity. Allergy. 2016 Jan 22. doi: 10.1111/all.12846.
31. Lucendo AJ. Cellular and molecular mechanisms in eosinophilic esophagitis: an updated overview of their clinical implications. Expert Rev Gastroenterol Hepatol. 2014;8:669-85.
32. Gonsalves N, Yang GY, Doerfler B, Ritz S, Ditto AM, Hirano I. Elimination diet effectively treats eosinophilic esophagitis

in adults; food reintroduction identifies causative factors. Gastroenterology. 2012;142:1451-9.
33. Lucendo AJ, Bellón T, Lucendo B. The role of mast cell in eosinophilic esophagitis. Pediatr Allergy Immunol. 2009;20:512-8.
34. Vicario M, Blanchard C, Stringer KF, Collins MH, Mingler MK, Ahrens A, Putnam PE, Abonia JP, Santos J, Rothenberg ME. Local B cells and IgE production in the oesophageal mucosa in eosinophilic oesophagitis. Gut. 2010;59:12-20.
35. Arias Á, Lucendo AJ, Martínez-Fernández P, González-Castro AM, Fortea M, González-Cervera J, Yagüe-Compadre JL, Mota-Huertas T, Vicario M. Dietary Treatment Modulates Mast Cell Phenotype, Density, and Activity in Adult Eosinophilic Esophagitis. Clin Exp Allergy. 2015. doi: 10.1111/cea.12504.
36. Echeverría Zudaire L, Fernández Fernández S, Rayo Fernández A, Bracamonte Bermejo T, Cilleruelo Pascual ML. No eficacia de omalizumab (Xolair) en el tratamiento de un paciente con esofagitis eosinofílica. Allergol Inmunopathol (Madr). 2008;36(extraordinario 1), 68-9.
37. Rocha R, Vitor AB, Trindade E, Lima R, Tavares M, Lopes J, Dias JA. Omalizumab in the treatment of eosinophilic esophagitis and food allergy. Eur J Pediatr. 2011;170:1471-4.
38. Clayton F, Fang JC, Gleich GJ, Lucendo AJ, Olalla JM, Vinson LA, Lowichik A, Chen X, Emerson L, Cox K, O'Gorman MA, Peterson KA. Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. Gastroenterology. 2014;147:602-9.
39. Molina-Infante J, Arias A, Barrio J, Rodríguez-Sánchez J, Sanchez-Cazalilla M, Lucendo AJ. Four-food group elimination diet for adult eosinophilic esophagitis: A prospective multicenter study. J Allergy Clin Immunol. 2014;134:1093-9.
40. Kagalwalla A, Amsden K, Makhija MM, Wechsler JB, Davis CM, Johnson K, Groetch M, Riffle ME, Manuel-Rubio M, Melin-Aldana H, Wershil BK, Collins MH, Chehade M. A multicenter study assessing the clinical, endoscopic and histologic response to four food elimination diet for the treatment of eosinophilic esophagitis. Gastroenterology. 2015;148:(Suppl 1), S-30.
41. Kagalwalla AF, Shah A, Li BU, Sentongo TA, Ritz S, Manuel-Rubio M, Jacques K, Wang D, Melin-Aldana H, Nelson S. Identification of specific foods responsible for inflammation in children with eosinophilic esophagitis successfully treated with empiric elimination diet. J Pediatr Gastroenterol Nutr. 2011;53:145-9.
42. Henderson CJ, Abonia JP, King EC, Putnam PE, Collins MH, Franciosi JP, Rothenberg ME. Comparative dietary therapy effectiveness in remission of pediatric eosinophilic esophagitis. J Allergy Clin Immunol. 2012;129:1570-8.
43. Kagalwalla AF, Amsden K, Shah A, Ritz S, Manuel-Rubio M, Dunne K, Nelson SP, Wershil BK, Melin-Aldana Cow's milk elimination: a novel dietary approach to treat eosinophilic esophagitis. J Pediatr Gastroenterol Nutr. 2012;55:711-6.
44. Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. Ann Allergy Asthma Immunol. 2014;113:624-9.
45. Kruszewski PG, Russo JM, Franciosi JP, Varni JW, Platts-Mills TA, Erwin EA. Prospective, comparative effectiveness trial of cow's milk elimination and swallowed fluticasone for pediatric eosinophilic esophagitis. Dis Esophagus. 2015. doi: 10.1111/dote.12339.
46. Lucendo AJ, Arias Á, Molina-Infante J. Efficacy of proton pump inhibitor drugs for inducing clinical and histological remission in patients with symptomatic esophageal eosinophilia: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2016;14:13-22.
47. Pentiuk S, Putnam PE, Collins MH, Rothenberg ME. Dissociation between symptoms and histological severity in pediatric eosinophilic esophagitis. J Pediatr Gastroenterol Nutr. 2009;48:152-60.
48. Lucendo AJ. Meta-Analysis-Based Guidance for Dietary Management in Eosinophilic Esophagitis. Curr Gastroenterol Rep. 2015;17:464.
49. Doerfler B, Bryce P, Hirano I, Gonsalves N. Practical approach to implementing dietary therapy in adults with eosinophilic esophagitis: the Chicago experience. Dis Esophagus. 2015;28:42-58.
50. Gonsalves N, Doerfler B, Hirano I. Long term maintenance therapy with dietary restriction in adults with eosinophilic esophagitis [abstract]. Gastroenterology. 2011;140(5, Suppl 1):S-180- 1.
51. Ngo P, Furuta GT, Antonioli DA, Fox VL. Eosinophils in the esophagus--peptic or allergic eosinophilic esophagitis? Case series of three patients with esophageal eosinophilia. Am J Gastroenterol. 2006;101:1666-70.
52. Sayej WN, Patel R, Baker RD, Tron E, Baker SS. Treatment with high-dose proton pump inhibitors helps distinguish eosinophilic esophagitis from noneosinophilic esophagitis. J Pediatr Gastroenterol. 2009;49:393-9.
53. Dranove JE, Horn DS, Davis MA, Kernek KM, Gupta SK. Predictors of response to proton pump inhibitor therapy among children with significant esophageal eosinophilia. J Pediatr. 2009;154:96-100.
54. Desai TK, Stecevic V, Chang CH, Goldstein NS, Badizadegan K, Furuta GT. Association of eosinophilic inflammation with esophageal food impaction in adults. Gastrointest Endosc. 2005;61:795-801.
55. Molina-Infante J, Ferrando-Lamana L, Ripoll C, Hernandez-Alonso M, Mateos JM, Fernandez-Bermejo M, Dueñas C, Fernandez-Gonzalez N, Quintana EM, Gonzalez-Nuñez MA. Esophageal eosinophilic infiltration responds to proton pump inhibition in most adults. Clin Gastroenterol Hepatol. 2011;9:110-7.
56. Moawad FJ, Veerappan GR, Dias JA, Baker TP, Maydonovitch CL, Wong RK. Randomized controlled trial comparing aerosolized swallowed fluticasone to esomeprazole for esophageal eosinophilia. Am J Gastroenterol. 2013;108:366-72.
57. Peterson KA, Thomas KL, Hilden K, Emerson LL, Wills JC, Fang JC. Comparison of esomeprazole to aerosolized, swallowed fluticasone for eosinophilic esophagitis. Dig Dis Sci. 2010;55:1313-9.
58. Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA. ACG clinical guideline: Evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Am J Gastroenterol. 2013;108:679-92.
59. Papadopoulou A, Koletzko S, Heuschkel R, Dias JA, Allen KJ, Murch SH, Chong S, Gottrand F, Husby S, Lionetti P, Mearin

ML, Ruemmele FM, Schäppi MG, Staiano A, Wilschanski M, Vandenplas Y; ESPGHAN Eosinophilic Esophagitis Working Group and the Gastroenterology Committee. Management guidelines of eosinophilic esophagitis in childhood. J Pediatr Gastroenterol Nutr. 2014;58:107-18.
60. Molina-Infante J, Katzka DA, Dellon ES. Proton pump inhibitor-responsive esophageal eosinophilia: a historical perspective on a novel and evolving entity. Rev Esp Enferm Dig. 2015;107:29-36.
61. Dellon ES, Speck O, Woodward K, Gebhart JH, Madanick RD, Levinson S, Fritchie KJ, Woosley JT, Shaheen NJ. Clinical and endoscopic characteristics do not reliably differentiate PPI-responsive esophageal eosinophilia and eosinophilic esophagitis in patients undergoing upper endoscopy: a prospective cohort study. Am J Gastroenterol. 2013;108:1854-60.
62. Warners MJ, van Rhijn BD, Curvers WL, Smout AJ, Bredenoord AJ. PPI-responsive esophageal eosinophilia cannot be distinguished from eosinophilic esophagitis by endoscopic signs. Eur J Gastroenterol Hepatol. 2015;27:506-11.
63. Moawad FJ, Schoepfer AM, Safroneeva E, Ally MR, Chen YJ, Maydonovitch CL, Wong RK. Eosinophilic oesophagitis and proton pump inhibitor-responsive oesophageal eosinophilia have similar clinical, endoscopic and histological findings. Aliment Pharmacol Ther. 2014;39:603-8.
64. Iwakura N, Fujiwara Y, Tanaka F, Tanigawa T, Yamagami H, Shiba M, Tominaga K, Watanabe T, Iijima K, Koike T, Walls AF, Arakawa T Basophil in filtration in eosinophilic oesophagitis and proton-pump inhibitor responsive oesophageal eosinophilia. Aliment Pharmacol Ther. 2015;41:776-84.
65. Moawad FJ, Wells JM, Johnson RL, Reinhardt BJ, Maydonovitch CL, Baker TP. Comparison of eotaxin-3 biomarker in patients with eosinophilic oesophagitis, proton pump inhibitor-responsive oesophageal eosinophilia and gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2015;42:231-8.
66. Wen T, Dellon ES, Moawad FJ, Furuta GT, Aceves SS, Rothenberg ME. Transcriptome analysis of proton pump inhibitor-responsive esophageal eosinophilia reveals proton pump inhibitor-reversible allergic inflammation. J Allergy Clin Immunol. 2015;135:187-97.
67. Molina-Infante J, Dueñas-Sadornil C, Rivas MD, Hernandez-Alonso M, Vinagre-Rodríguez G, Mateos-Rodríguez JM, Dueñas-Sadornil C, Perez-Gallardo B, Ferrando-Lamana L, Fernandez-Gonzalez N, Bañares R, Zamorano J. Proton pump inhibitor-responsive oesophageal eosinophilia correlates with downregulation of eotaxin-3 and Th2 cytokines overexpression. Aliment Pharmacol Ther. 2014;40:955-65.
68. Lucendo AJ, Arias A, González-Cervera J, Olalla JM, Molina-Infante J. Dual response to dietary/topical steroid and proton pump inhibitor therapy in adult patients with eosinophilic esophagitis. J Allergy Clin Immunol. 2015; (in press).
69. Sodikoff J, Hirano I. Proton pump inhibitor-responsive esophageal eosinophilia does not preclude food-responsive eosinophilic esophagitis. J Allergy Clin Immunol. 2015. doi: 10.1016/j.jaci.2015.07.008.
70. Molina-Infante J, Bredenoord AJ, Cheng E, Dellon ES, Furuta GT, Gupta SK, Hirano I, Katzka DA, Moawad FJ, Rothenberg ME, Schoepfer A, Spechler SJ, Wen T, Straumann A, Lucendo AJ; From the PPI-REE Task Force of the European Society of Eosinophilic Oesophagitis (EUREOS). Proton pump inhibitor-responsive oesophageal eosinophilia: an entity challenging current diagnostic criteria for eosinophilic oesophagitis. Gut. 2015 Dec 18. doi: 10.1136/gutjnl-2015-310991.
71. Molina-Infante J, Martinek J, Martinez-Alcala C, Krajciova J, Moawad FJ, Dellon ES. Long-term efficacy of PPI therapy in patients with PPI-responsive esophageal eosinophilia: an international multicenter study. Gastroenterology. 2014;146:(5, Suppl):S-17.
72. Gutiérrez-Junquera C, Fernández-Fernández S, Cilleruelo ML, et al. High prevalence of response to proton pump inhibitor treatment in children with esophageal eosinophilia. J Pediatr Gastroenterol Nutr Published Online First 23 Oct 2015. doi: 10.1097/MPG.0000000000001019.
73. Schaefer ET, Fitzgerald JF, Molleston JP, Croffie JM, Pfefferkorn MD, Corkins MR, Lim JD, Steiner SJ, Gupta SK. Comparison of oral prednisone and topical fluticasone in the treatment of eosinophilic esophagitis: a randomized trial in children. Clin Gastroenterol Hepatol. 2008;6:165-73.
74. Sawas T, Dhalla S, Sayyar M, Pasricha PJ, Hernaez R. Systematic review with meta-analysis: pharmacological interventions for eosinophilic oesophagitis. Aliment Pharmacol Ther. 2015;41:797-806.
75. Chuang MY, Chinnaratha MA, Hancock DG, Woodman R, Wong GR, Cock C, Fraser RJ. Topical steroid therapy for the treatment of eosinophilic esophagitis (EoE): a systematic review and meta-analysis. Clin Transl Gastroenterol. 2015;6:e82.
76. Tan ND, Xiao YL, Chen MH. Steroids therapy for eosinophilic esophagitis: systematic review and meta-analysis. J Dig Dis. 2015. doi: 10.1111/1751-2980.12265.
77. Dellon ES, Sheikh A, Speck O, Woodward K, Whitlow AB, Hores JM, Ivanovic M, Chau A, Woosley JT, Madanick RD, Orlando RC, Shaheen NJ. Viscous topical is more effective than nebulized steroid therapy for patients with eosinophilic esophagitis. Gastroenterology. 2012;143:321-4.
78. Miehlke S, Hruz P, Vieth M, Bussmann C, von Arnim U, Bajbouj M, Schlag C, Madisch A, Fibbe C, Wittenburg H, Allescher HD, Reinshagen M, Schubert S, Tack J, Müller M, Krummenerl P, Arts J, Mueller R, Dilger K, Greinwald R, Straumann A. A randomised, double-blind trial comparing budesonide formulations and dosages for short-term treatment of eosinophilic oesophagitis. Gut. 2015. doi: 10.1136/gutjnl-2014-308815.
79. Tomizawa Y, Melek J, Sakuraba A. Comparison of Efficacy of Pharmacologic Therapy of Eosinophilic Esophagitis (EoE): A Systematic Review and Network Meta-Analysis. Gastroenterology. 2015;148 (4, Suppl 1):S-792.
80. Straumann A, Conus S, Degen L, Frei C, Bussmann C, Beglinger C, Schoepfer A, Simon HU. Long-term budesonide maintenance treatment is partially effective for patients with eosinophili esophagits. Clin Gastroenterol Hepatol. 2011; 9(5):400-9.
81. Lindberg GM, Van ER, Saboorian MH. A case of herpes esophagitis after fluticasone propionate for eosinophilic esophagitis. Nat Clin Pract Gastroenterol Hepatol. 2008;5:527-30.
82. Machicado JD, Younes M, Wolf DS. An unusual cause of odynophagia in a patient with eosinophilic esophagitis. Gastroenterology. 2014;147:37-8.

83. Muley P, Shah M, Muley A. Safety of inhaled fluticasone propionate therapy for pediatric asthma - a systematic review. Curr Drug Saf. 2015;8:186-94.
84. Harel S, Hursh BE, Chan ES, Avinashi V, Panagiotopoulos C. Adrenal Suppression in Children Treated With Oral Viscous Budesonide for Eosinophilic Esophagitis: A Pilot Study. J Pediatr Gastroenterol Nutr. 2015;61:190-3.
85. Aceves SS, Bastian JF, Newbury RO, Dohil R. Oral viscous budesonide: a potential new therapy for eosinophilic esophagitis in children. Am J Gastroenterol. 2007;102:2271-9.
86. Dohil R, Newbury R, Fox L, Bastian J, Aceves S. Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. Gastroenterology. 2010;139:418-29.
87. Philla KQ, Min SB, Hefner JN, Howard RS, Reinhardt BJ, Nazareno LG, Vogt KS. Swallowed glucocorticoid therapy for eosinophilic esophagitis in children does not suppress adrenal function. J Pediatr Endocrinol Metab. 2015;28:1101-6.
88. Straumann A, Bussmann C, Conus S, Beglinger C, Simon HU. Anti-TNF-alpha (infliximab) therapy for severe adult eosinophilic esophagitis. J Allergy Clin Immunol. 2008;122:425-7.
89. Assa'ad AH, Gupta SK, Collins MH, Thomson M, Heath AT, Smith DA, Perschy TL, Jurgensen CH, Ortega HG, Aceves SS. An antibody against IL-5 reduces numbers of esophageal intraepitelial eosinophils in children with eosinophilic esophagitis. Gastroenterology. 2011;141:1593-604.
90. Straumann A, Conus S, Grzonka P, Kita H, Kephart G, Bussmann C, Beglinger C, Smith DA, Patel J, Byrne M, Simon HU. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. Gut. 2010;59:21-30.
91. Spergel JM, Rothenberg ME, Collins MH, Furuta GT, Markowitz JE, Fuchs G 3rd, O'Gorman MA, Abonia JP, Young J, Henkel T, Wilkins HJ, Liacouras CA. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. J Allergy Clin Immunol. 2012;129:456-63.
92. Rothenberg ME, Wen T, Greenberg A, Alpan O, Enav B, Hirano I, et al. Intravenous anti-IL-13 mAb QAX576 for the treatment of eosinophilic esophagitis. J Allergy Clin Immunol. 2015;135:500-7.
93. Chehade M, Sampson HA, Morotti RA, Magid MS. Esophageal subepithelial fibrosis in children with eosinophilic esophagitis. J Pediatr Gastroenterol Nutr. 2007;45:319-28.
94. Aceves SS, Newbury RO, Dohil R, Bastian JF, Broide DH. Esophageal remodeling in paediatric eosinophilic esophagitis. J Allergy Clin Immunol. 2007;119:206-12.
95. Lucendo AJ, Arias A, De Rezende LC, Yague-Compadre JL, Mota-Huertas T, Gonzalez-Castillo S, Cuesta RA, Tenias JM, Bellón T. Subepithelial collagen deposition, profibrogenic cytokine gene expression, and changes after prolonged fluticasone propionate treatment in adult eosinophilic esophagitis: a prospective study. J Allergy Clin Immunol. 2011;128:1037-46.
96. Schoepfer AM, Safroneeva, Bussmann C, Kuchen T, Portmann S, Simon HU, Straumann A. Delay in Diagnosis of Eosinophilic Esophagitis Increases Risk for Stricture Formation, in a Time-Dependent Manner. Gastroenterology. 2013;145:1230-6.
97. Dellon ES, Gibbs WB, Rubinas TC, Fritchie KJ, Madanick RD, Woosley JT, Shaheen NJ. Esophageal dilation in eosinophilic esophagitis: safety and predictors of clinical response and complications. Gastrointest Endosc. 2010;71:706-12.
98. Schoepfer AM, Gonsalves N, Bussmann C, Conus S, Simon HU, Straumann A, Hirano I. Esophageal dilation in eosinophilic esophagitis: effectiveness, safety, and impact on the underlying inflammation. Am J Gastroenterol. 2010;105:1062-70.
99. Moawad FJ, Cheatham JG, Dezee KJ. Meta-analysis: the safety and efficacy of dilation in eosinophilic oesophagitis. Aliment Pharmacol Ther. 2013;38:713-20.
100. Kavitt RT, Ates F, Slaughter JC, Higginbotham T, Shepherd BD, Sumner EL, Vaezi MF. Randomized controlled trial comparing esophageal dilation to no dilation among adults with esophageal eosinophilia and dysphagia. Dis Esophagus. 2015. doi: 10.1111/dote.12398. 2015.
101. Kavitt RT, Penson DF, Vaezi MF. Eosinophilic esophagitis: dilate or medicate? A cost analysis model of the choice of initial therapy. Dis Esophagus. 2014;27:418-23.
102. Lipka S, Keshishian J, Boyce HW, Estores D, Richter JE. The natural history of steroid-naïve eosinophilic esophagitis in adults treated with endoscopic dilation and proton pump inhibitor therapy over a mean duration of nearly 14 years. Gastrointest Endosc. 2014;80:592-8.
103. Kaplan M, Mutlu EA, Jakate S, Bruninga K, Losurdo J, Losurdo J, Keshavarzian A. Endoscopy in eosinophilic esophagitis: "feline" esophagus and perforation risk. Clin Gastroenterol Hepatol. 2003;1:433-7.
104. Lucendo AJ, De Rezende L. Endoscopic dilation for treatment of eosinophilic esophagitis: a strategy with a high perforation risk. Endoscopy. 2007;39:376.
105. Cohen MS, Kaufman AB, Palazzo JP, Nevin D, Dimarino AJ, Jr., Cohen S. An audit of endoscopic complications in adult eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2007;5:1149-53.
106. Straumann A, Bussmann C, Zuber M, Vannini S, Simon HU, Schoepfer A. Eosinophilic Esophagitis: Analysis of Food Impaction and Perforation in 251 Adolescent and Adult Patients. Clin Gastroenterol Hepatol. 2008;11:598-600.
107. Jung KW, Gundersen N, Kopacova J, Arora AS, Romero Y, Katzka D, Francis D, Schreiber J, Dierkhising RA, Talley NJ, Smyrk TC, Alexander JA. Occurrence of and risk factors for complications after endoscopic dilation in eosinophilic esophagitis. Gastrointest Endosc. 2011;73:15-21.
108. Jacobs JW Jr, Spechler SJ. A systematic review of the risk of perforation during esophageal dilation for patients with eosinophilic esophagitis. Dig Dis Sci. 2010;55:1512-5.
109. Reimer C. Safety of long-term PPI therapy. Best Pract Res Clin Gastroenterol. 2013;27:443-54.

Alfredo J Lucendo

Department of Gastroenterology
Hospital General de Tomelloso
Vereda de Socuéllamos, s/n
13700 Tomelloso (Ciudad Real), Spain
E-mail: alucendo@vodafone.es