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REVIEW

Treatment of eosinophilic esophagitis in the pediatric patient: an evidence-based approach

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Abstract

Eosinophilic esophagitis (EoE) is a unique form of non-IgE-mediated food allergy characterized by esophageal eosinophilic infiltration that commonly causes dysphagia and food impaction in children and adolescents. Assessing the efficacy of dietary restrictions or drug therapies to achieve clinical and histologic resolution of EoE through randomized controlled trials and meta-analyses has resulted in new evidence-based guidelines. Avoiding food triggers is the only therapy targeting the cause of the disease. None of the currently available food allergy tests adequately predict food triggers for EoE. Exclusively feeding with an amino acid-based elemental diet and empiric six-food elimination diet (avoiding the six foods most commonly related with food allergy) has consistently provided the best cure rates, but their high level of restriction and need for multiple endoscopies are deterrents for implementation. Simpler and less restrictive empirical methods, like a four-food (milk, gluten-containing cereals, egg, legumes) or a two-food (milk and gluten) elimination diet, show encouraging results. Proton pump inhibitors are currently a first-line treatment, achieving histological remission and improvement of symptoms in 54.1 and 64.9% of pediatric EoE patients, respectively. The efficacy of topical corticosteroids in EoE assessed in several trials and summarized in meta-analyses indicates that budesonide and fluticasone propionate are significantly superior to placebos, both in decreasing eosinophil mucosal infiltration and in relieving symptoms. Owing to differences in drug delivery, viscous budesonide formulas seem to be the best pharmacological therapy for EoE.

Conclusion: Applying evidence-based therapies and a practical management algorithm provide an effective control of EoE.

What is Known:

- *Eosinophilic esophagitis (EoE) now constitutes the main cause of dysphagia and food impaction in children, adolescents, and young adults.*
- *Its chronic course and frequent progression to subepithelial fibrosis leading to strictures and narrow-caliber esophagus indicate the need for treatment.*

What is New:

- *Therapeutic goals in children with EoE include resolution of esophageal symptoms, to cure esophageal inflammation (mucosal healing) and restore a proper esophageal caliber in case of fibrostenotic endoscopic findings. Avoiding iatrogenic drug effects and nutritional deficiencies, as well as maintaining an adequate quality of life, is also essential.*
- *Novel evidence-based guidelines, endorsed by several European scientific societies, incorporate recent advances in knowledge from several randomized controlled trials and systematic reviews to provide the best standard of care to pediatric patients, by following simple management algorithms.*

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Keywords Eosinophilic esophagitis · Diet therapy · Drug therapy · Dilation · Glucocorticoids · Proton pump inhibitors · Disease management

Abbreviations

AGA	American Gastroenterological Association
DSQ	Dysphagia Symptom Questionnaire
EEsAI	Eosinophilic Esophagitis Activity Index
EoE	Eosinophilic esophagitis
FFED	Four-food elimination diet
GERD	Gastroesophageal reflux disease
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HPF	High-powered field
NASPGHAN	North American Society of Gastroenterology, Hepatology and Pediatric Nutrition
PEESS	Pediatric Eosinophilic Esophagitis Symptom Score
RCT	Randomized controlled trial
SFED	Six-food elimination diet
TFED	Two-food elimination diet

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 [59]. After its characterization in the early 1990s as a distinct clinicopathological disorder [10], the frequency of EoE has risen sharply in the last two decades to constitute now the most prevalent cause of chronic or recurrent esophageal symptoms after gastroesophageal reflux disease (GERD) and the main cause of dysphagia and food impaction in children, adolescents, and young adults in Europe and North America [7], where it affects 1 per 2000 inhabitants [81]. However, EoE is now also emerging in other regions including Central and South America [19, 95], North Africa [9, 39], and Asia [44]. The natural history of EoE consists of a chronic inflammation that may progress into fibrous remodeling of the esophageal wall, with collagen deposition, lamina propria fibrosis, and development of esophageal strictures, as the disease evolves from childhood into adulthood [24, 50, 102]. In younger children and infants, the most common symptoms reported are reflux-like symptoms, vomiting, abdominal pain, food refusal, and failure to thrive. Older children and adults with EoE most commonly report solid food dysphagia, food impaction, and nonswallowing-associated chest pain [54]. Although not associated with mortality or risk of malignancy, the chronic and progressive nature of EoE and associated symptoms negatively impacts on the quality of life of patients [60].

The amount of scientific evidence available on epidemiologic, pathophysiological, clinical, and therapeutic aspects of the disease has grown exponentially throughout the two-decade history of EoE and was summarized in up to four consensus documents and clinical practice guidelines [22, 31, 49, 87]. In recent years, relevant advances, including the clarification of the relationship between gastroesophageal reflux and EoE, the abandonment of proton pump inhibitor-responsive esophageal eosinophilia as a diagnostic category [77], and the results from several randomized controlled trials (RCTs) and systematic reviews with meta-analyses, determined that these are currently outdated [61]. New guidelines developed by an international group of experts using the GRADE system under the support of the United European Gastroenterology and endorsed by several scientific societies [59] provide recommendations to clinicians who care for children and adults with EoE based on the best evidence and with a structured framework for diagnosing and treating patients with EoE.

The aims of this review are to provide an evidence-based overview of the efficacy of the therapeutic options available for treating children with EoE, as well as to discuss their ease of use, advantages, and limitations. Since EoE currently represents a growing chronic health problem that, due to its prevalence, is becoming a significant burden for several healthcare systems, updated knowledge on the part of all actors involved in the healthcare process is needed to successfully treat children with EoE.

Treatment goals in EoE: from the origins to the evidence

The first clinical guidelines on EoE were published in 2007 based on the consensus of experts from the American Gastroenterological Association (AGA) and the North American Society of Gastroenterology, Hepatology and Pediatric Nutrition (NASPGHAN) [31]. Thereafter, all the subsequent guidelines consensually defined EoE as a clinicopathological disorder characterized by symptoms related to esophageal dysfunction, together with a dense eosinophil-predominant infiltration of the esophageal surface. Both features are required to provide a diagnosis, and neither should be considered in isolation [31, 59]. As a result, all consensus documents agreed that the goal of therapy in EoE should include not only symptomatic improvement but also histological remission of the disease, in order to avoid the long-term complications derived from fibrous remodeling and deterioration in health-related quality of life. From the outset, it was

made clear that therapeutic goals also included preventing adverse effects related to pharmacological therapy and avoiding nutritional deficiencies derived from dietary restriction, especially among pediatric populations.

Regarding symptoms, several instruments have been validated to accurately measure dysphagia and feeding difficulties in adults (two instruments) and children (one instrument), which should be incorporated into an EoE management protocol. For adults, the EoE Activity Index (EEsAI) quantifies the difficulties foreseen by patients with different food consistencies, as well as dietary or behavioral modifications for the same food consistencies [103]; the Dysphagia Symptom Questionnaire (DSQ) is a three-item daily electronic diary that records solid food avoidance days, dysphagia days, and actions taken to get relief [23]. For children, the Pediatric EoE Symptom Score (PEESS v2.0) is a questionnaire of 20 items which are consolidated into four major areas (dysphagia, GERD, nausea/vomiting, and pain). It was developed in an effort to identify and uniquely measure relevant outcomes that patients and their families considered important [29]. The PEESS v2.2 has recently demonstrated a weak but statistically significant correlation with histopathologic and molecular features of the disease [63].

The diagnostic threshold for eosinophil density in EoE has been defined in 15 eosinophils/high-powered field (hpf) (standard size of around 0.3 mm^2) in esophageal mucosa, taken as the peak concentration in the specimens examined. This threshold reliably distinguishes between EoE and GERD with a sensitivity of 100% and a specificity of 96% for the diagnosis of EoE [25]. Consequently, the criterion of histological remission most commonly used in the various studies was an eosinophilic concentration below the diagnostic threshold in all esophageal biopsies. However, until now, it has not been possible to establish a consensual or uniform criterion to define, from a histological point of view, when a patient has EoE in remission. Therefore, remission criteria have widely varied among the different authors, to include < 15, < 10, and < 5 eosinophils/hpf [4, 40, 56, 66], or even the percentage of reduction regarding the baseline peak eosinophil count [96, 110]. Recent prospective data in adults show that a response cutpoint of < 15 eosinophils/hpf identified most patients with symptom and endoscopic improvements. Lowering this threshold to < 5 eosinophils/hpf did not result in a substantial additional symptom or endoscopy improvement in a clinical practice setting [92].

After evaluating several cutoff values, the symptomatic indices are not precise enough to predict the histological or even endoscopic remission of the EoE [63, 97]; thus, the independent assessment of both symptoms and histology is essential to have an accurate evaluation of EoE in a patient. Therefore, physicians should not make assumptions about the biological activity of EoE relying exclusively on the symptoms [53]. Despite this, a recent study conducted in adult EoE patients highlighted that gastroenterologists still rate EoE activity mainly on the basis of endoscopic findings and symptoms and, to a lesser extent, on histologic assessment [104]. Less invasive alternative procedures for diagnosing and monitoring EoE have been largely pursued because of the invasiveness of taking biopsies, and these are urgently needed in pediatric populations, who are less willing to undergo repeated endoscopies and biopsies in order to monitor the disease and the response to therapy.

Dietary therapy

Avoiding the intake of the "trigger" food constitutes the first line of treatment in multiple manifestations of food allergy, from celiac disease to food-induced anaphylaxis. In this sense, dietary therapy is the only one targeting the cause of the disease and thus represents a first-line treatment option for patients with EoE. However, the different approaches proposed have shown dramatic differences in terms of its effectiveness to induce disease remission and its likelihood of being maintained as a long-term therapy option.

Any kind of dietary intervention in EoE aims to achieve remission of the disease (in terms of symptoms, but specially in histology) as a reference point. This initially involves identification of the specific food/s that triggers EoE by demonstrating recurrence of inflammation. Over the last decade, different authors have tried to achieve this goal through different dietary approaches that have evolved as our knowledge of the disease increased. The goal of dietary therapy in EoE is to identify and to exclude from the diet only the specific food(s) responsible for triggering and maintaining the disease in each individual patient [78].

Exclusive feeding with elemental diets: the origins of dietary therapy in EoE

The first evidence on the efficacy of a dietary intervention in inducing remission of EoE was published in 1995 by Kelly et al. [43]. They used an amino acid-based formula to feed a series of 10 children with severe eosinophilic infiltration of the esophagus that had initially been attributed to gastroesophageal reflux disease and was refractory to other therapies, including H2 antihistamines, prokinetic drugs, and even funduplication in six out of them. After a minimum of 6 weeks of exclusively feeding the patients with this nonantigenic formula completely devoid of proteins, 8 children were disease free and the remaining two showed symptomatic improvement and a significant reduction in the eosinophilic infiltrate. The disease recurred early after patients returned to a regular diet.

This seminal paper defined refractory esophagitis with severe eosinophilia as a particular form of food allergy instead of a manifestation of gastroesophageal reflux and placed the

esophagus for the first time as an organ susceptible to inflammation as a consequence of an allergic reaction to food proteins, as well as to the exposure to irritants like gastric reflux.

The high effectiveness of elemental formulas was confirmed repeatedly in subsequent retrospective reports carried out in both children and adolescents with EoE [40, 48, 62] and later prospectively in adults [89, 121]. Elemental diets demonstrated an overall efficacy to induce histological remission of EoE (i.e., a reduction in peak eosinophil counts to < 15 per HPF) of 90.8% (95% CI 84.7–95.5%), according to the results of a meta-analysis of 13 studies including 429 EoE patients (411 children and 18 adults) [6].

Despite elemental diets outperforming all other dietary-based and most drug-based strategies available in terms of inducing histological remission of EoE [70], their use in clinical practice is inhibited by several disadvantages linked to being exclusively fed by an artificial formula long term. The palatability of the elemental formula is poor and this represents a serious limitation for its use, and led to a nasogastric tube placement in 80% of the children included in one of the largest studies [48]. Adherence to an exclusive elemental diet that requires avoiding all kinds of table foods represented a challenge for adult patients with EoE, and up to one third of them were unable to adhere to the diet in a 4-week trial [89]. Although no study has systematically assessed adherence to diet in children, variability in terms of effectiveness makes it possible for some patients to have consumed other foods in addition to the elemental formulas, preventing the achievement of 100% effectiveness. Airborne allergens have also been involved as EoE triggers in a minority of patients [107], thus contributing to a nonuniversal efficacy of this dietary option.

Apart from its poor palatability, limitations of exclusive feeding with elemental diet also include its high cost, not universally covered by health insurances, and the possibility of delayed speech onset in young children as a result of undeveloped facial muscles from an exclusive liquid diet, requiring no chewing [5, 52]. In addition, removing all food during the first 3 years of life may impact on taste preferences and impede or delay the acquisition of feeding skills, since the key developmental milestones for feeding are achieved within this early period of life [20]. Despite its high effectiveness, the identification of specific food triggers after an elemental diet might be unfeasible due to the large number of endoscopies that should be performed.

Due to the impracticality of implementing elemental diets over a long period, they do not constitute a proper nutritional alternative for a chronic disease like EoE. The only real utility of this diet in clinical practice is in treating small children not yet on solid foods, who have persistent symptoms and inflammation, especially if a rapid clinical improvement is required [52]. Using an elemental formula as a temporary supplement option in patients under extensive dietary restriction has been assessed in the adult literature [56]. Finally, exclusive feeding with an elemental diet as an ultimate rescue therapy for patients who have failed all other dietary alternatives has been proposed [82], but no real data from clinical research supports its use in this scenario so far.

Allergy test-driven food elimination: the allergists go on stage

The demonstration that EoE as a specific form of food allergy that went into remission after avoiding exposure to foods completely by exclusive amino acid-based elemental formula led allergists to try to identify the food or foods responsible for the disease through skin allergy tests, including both skin prick tests (SPTs) and atopy patch tests (APTs) and serum-specific IgE testing.

The first assessment of a food allergy testing-based elimination diet was published in 2002 and eliminated from patients' diets those foods with positive results on SPT and APT [109]. After excluding an average of five foods, clinic and histologic remission was induced in 49% of pediatric patients. Causative foods were exclusively attributed by symptom recurrence after food reintroduction, as noted by parents, with no biopsy evaluation. A decade later, the same research group updated their results with an overall efficiency of 53% [111]. Other authors that have assessed the same strategy in patients of all ages obtained wide variable results [37, 73], which were summarized in a systematic review with meta-analysis [6] revealing that, overall, this dietary approach led to histologic remission in 45.5% of patients (95% CI 35.4–55.7%), with wide heterogeneity (I^2 75%) indicating a low reproducibility. The efficacy rates were significantly higher among children than in adults (47.9 vs. 32.2%, respectively) but low enough to exclude the effect of chance if we consider that food sensitivities against common foods are frequent especially in children [88] and that EoE is usually triggered by commonly consumed foods.

More recently, a pilot study in adults that evaluated an elimination diet guided by blood IgE microarrays (e.g., measuring IgE levels to food protein components) was interrupted early due to poor efficacy (7% histologic remission) [119]. Sensitivity of APT for identified food triggers by food elimination diet in adults with EoE was only 5.9% in a recent pilot study, thus providing an extremely poor reliability [27]. The combination of multiple allergy skin and blood tests, measuring either immediate or delayed hypersensitivity responses, failed in detecting offending foods in adult EoE patients [91]. As a consequence of the consistently low utility of allergy tests in the identification of food triggers of EoE in patients of all ages, a consensus document released by the European Academy of Allergy, Asthma and Immunology considered skin allergy test results insufficient to design effective diets for EoE patients, or to support the development of dietary advancement in EoE

[106]. Accordingly, the new evidence-based guidelines for diagnosis and management of EoE do not recommend allergy testing-directed food elimination as it induces histologic remission of EoE in less than one third of adult patients and only a slightly higher rate in pediatric ones [59].

Empiric elimination of common dietary antigens in the treatment of EoE to identify specific food triggers for EoE

As with other dietary interventions for EoE, empiric elimination diets were firstly assessed in children as an attempt to overcome the many disadvantages of exclusively feeding patients with elemental formulas and because of the low sensitivity and specificity of skin allergy tests to identify the food(s) responsible for EoE. With no previous allergy tests performed, Amir Kagalwalla, a pediatrician from Chicago, proposed empirically removing the six most common foods related to food allergy from patients' diets: milk protein, wheat, eggs, soy, peanuts/tree nuts, and fish/seafood. The effectiveness of the "six-food elimination diet (SFED)" was firstly assessed in 35 children after a 6-week period and demonstrated resolution of the eosinophilic infiltration (defined as a decrease to < 10 cells/hpf) in esophageal biopsies in 26 patients (74%) and a partial remission (< 20 eosinophils/hpf) in three others [40]. Sequential reintroduction of foods previously excluded, followed by repeated endoscopy and biopsies, could clearly identify the exact food triggering EoE in each particular patient [41]. Since then, several studies have documented equal effectiveness rates for a SFED in children [37] and adults [34, 56, 91]. The overall effectiveness of empiric SFED to induce remission of eosinophilic infiltration in EoE below the diagnostic threshold was 72% (95% CI 66–78%), according to a meta-analysis of seven studies including 75 children and 122 adults treated [6]. Notably, the results of the various studies have shown a high concordance in the remission rate (with a heterogeneity measure with I^2 statistic of 0% in the aforementioned meta-analysis).

As specific food triggers for EoE, milk, wheat/gluten-containing cereals, and egg have been attributed to causing the disease in up to 50% of cases, with extremely consistent results among the several studies available with food reintroduction, and no differences between children [37, 41] and adults [34, 56], or between European [56, 74], North American [34, 41, 123], and Australian [91] research, were found. Common nutritional habits, derived from a similar agricultural and culinary culture, explain these similarities. Other foods, like legumes, soy, and fish/seafood, have shown different frequencies between studies from different geographical regions, which has been explained by differences in food consumption patterns and sensitization profiles between Spain and the USA, for example. Table 1 presents the relative frequencies with which each EoE food trigger has been identified in different studies. The number of foods responsible for triggering and maintaining EoE has varied little among different studies, with a usual number between 1 and 3 in each patient [52]. The fact that the studies in the USA did not completely reintroduce all foods previously excluded [34], or that once the first food responsible for EoE had been identified, not continuing the study, in the case of children [41], prevents comparisons with the results of European studies.

Of note, the majority (45–85%) of patients responding to a SFED were found to have just one or two causative foods after six food challenges and endoscopies [59]. The SFED represented a milestone in the therapeutic approach of EoE, allowing for the first time a moderate to high effectiveness intervention, and with the capacity to identify the foods responsible for EoE in the responders, a drug-free long-term remission. However, there are several drawbacks, namely the high level of dietary restriction and the large number of endoscopies required to identify specific culprit food/s after individual food reintroduction [59]. As the most common causative foods identified after a response to a SFED have been cow's milk, wheat/gluten-containing cereals, egg, and, to a lesser extent, soy/legumes, with a negligible role for nuts, fish, and seafood, the development of a four-food elimination diet (FFED), avoiding the most common food triggers in EoE (cow's milk, wheat, eggs, and legumes), was warranted. After a first prospective multicenter study in adult patients carried out in Spain that showed a 54% remission rate [74], the corresponding multicenter study carried out in US children has recently been published [42]. The authors recruited, from four medical centers, 78 children with PPI-refractory EoE who were instructed to exclude cow's milk, wheat, egg, and soy from their diet. After 8 weeks, clinical, endoscopic, and histologic assessments were made, and 50 patients (64%) were in histologic remission (peak eosinophil count < 15 eosinophils/hpf); symptoms scores decreased in parallel. After sequential food reintroduction, the most common food triggers that induced histologic inflammation in the 25 patients who completed food reintroduction were cow's milk (84%), egg (28%), wheat (8%), and soy (8%). One single food trigger inducing recurrence of esophageal inflammation was identified in 62%, with cow's milk-induced EoE being present in 88% of these patients. Comparatively, half of adult responders to a FFED were found to have cow's milk, wheat, or both as food triggers [74], indicating differences in sensitization patterns or in food consumption habits among patients of different ages.

Accordingly, a step-up approach (in other words, eliminating at first the one or two most common food triggers and subsequently increasing the level of restriction in nonresponders) was the next logical step to be assessed in the empiric dietary therapy of EoE. Establishing a parallel with the "step-up" and "top down" strategies to manage Crohn's

Table 1 Summary of the results of prospective studies on empiric six- (SFED), four- (FFED), or two- (TFED) food group elimination diets FFED, showing the number and the most common food triggers identified through individual food reintroduction

First author, year of publication, country	Diet population	Histologic remission rate (%)	Number of culprit foods identified through individual reintroduction of either six, four, or two food groups			Most common food triggers identified through individual food reintroduction
			1 (%)	2 (%)	> 2 (%)	
Kagalwalla, 2011, USA [41]	SFED Children Single center	74	72	8	8	Milk 74% Wheat 26% Eggs 17%
Gonsalves, 2012, USA [34]	SFED Adults Single center	70	85	15		Wheat 60% Milk 50%
Lucendo, 2013, Spain [56]	SFED Adults Single center	72	36	31	33	Milk 62% Wheat/gluten 29% Egg 26% Legumes 24%
Molina-Infante, 2014, Spain [74]	FFED Adults Multicenter	54	45	45	–	Milk 50% Egg 36% Wheat/gluten 31% Legumes 18%
Philpott, 2016, Australia [91]	SFED Adults Single center	–	56	17	13	Milk 43% Wheat 43% Eggs 34%
Kagalwalla, 2017, USA [42]	FFED Children Multicenter	64	64	20	16	Milk 85% Egg 35% Wheat 33% Soy 19%
Molina-Infante, 2018, Spain [80]	TFED Adults and children Multicenter	43	58	33	9	Milk 81% Wheat/gluten 43% Egg 15% Legumes 9%

disease [79], the recently published "2-4-6 study" proposes starting empiric food elimination by avoiding the consumption of the two most common food triggers for EoE (milk and gluten), a FFED in case of persistent esophageal inflammation, and keeping the SFED as a final rescue alternative for nonresponders [80]. This prospective study conducted in 14 European centers is also the first one in enrolling a large series of 130 patients with EoE of all ages (105 adults and 25 children) unresponsive to PPIs. A two-food elimination diet (TFED) was undertaken with all patients, and 56 (43%) of them achieved clinicohistologic remission. Remission rates with FFED and SFED were 60 and 79%, respectively, with no differences between children and adults. A single food trigger was identified in 58% of cases, milk in 52%, and gluten-containing grains in 16%. Two food triggers were present in 33% of the whole series. As an additional advantage, this step-up empiric elimination diet also allowed early identification of a majority of patients with EoE who responded to empiric diets with few food triggers, because overall, 55 of 60 (91.6%) of the responders to a TFED/FFED had only one or two food triggers and were appropriate candidates to a long-term maintenance dietary treatment.

Finally, a step-up strategy reduced endoscopic procedures and diagnostic process time by 20% as compared with starting the food trigger identification process by an initial SFED.

Topic steroid therapy

From the initial description of the disease in the literature, systemic steroids were demonstrated to be capable of rapidly inducing clinical and histologic remission of the disease [47]. Simultaneously, topically administered steroids with reduced bioavailability (fluticasone propionate and beclomethasone), swallowed instead of inhaled, proved to be equally effective in inducing clinical and histological remission in a short series of four children aged between 12 and 13 years old [28]. Later on, topic swallowed steroids were shown to have the same effect as oral prednisone in RCT [100]. Swallowed fluticasone propionate (2 puffs 4 times/day; 110 mcg per puff for ages 1–10 years and 220 mcg per puff for ages 11 years or older) showed the same effectiveness in inducing clinical and histologic remission of EoE compared with oral prednisone (1 mg/kg/dose twice a day) after 4 weeks of use. As a consequence,

they have now replaced systemic corticosteroids for the treatment of EoE, since the latter presents no advantages in terms of symptom resolution, relapse rates, or time to relapse, but is associated with significantly more severe adverse effects. On this basis, systemic steroids are not recommended in EoE [59], and their use is restricted to emergency situations with severe dysphagia or significant weight loss.

In the last 2 years, up to four systematic reviews with meta-analysis have summarized the evidence from available RCTs on the efficacy of topic corticosteroids to induce remission of EoE [15, 83, 98, 116], and one more has compared its effectiveness with that of PPIs [51]. Overall, both budesonide and fluticasone propionate were shown to be significantly superior to placebo in decreasing eosinophil density in the esophageal mucosa [15, 116]. In parallel, symptom relief was also significantly more frequent in patients who received corticosteroids than in the placebo group [98].

Subgroup analyses that included only RCTs carried out in children demonstrated that swallowed topical steroids were, overall, significantly superior to placebo in inducing histological remission of EoE, including both reduction in peak eosinophil densities below the diagnostic threshold of 15 cells/hpf (OR 24.6; 95% CI 7, 86.8) [98] and in achieving complete histological response (OR 14.8; 95% CI 3.2, 69.2) [83]. Regarding symptoms, swallowed topical steroids overall were superior to placebo in inducing any improvement in dysphagia scores, despite not having statistically significant differences (OR 3.54; 95% CI 0.89, 14.09) [98]. When children treated with fluticasone propionate and budesonide were analyzed separately, budesonide was significantly superior to placebo in terms of symptomatic relief (OR 7.20; 95% CI 2.15, 24.05) but not fluticasone propionate (OR 1.27; 95% CI 0.44, 3.65) [83].

The several doses of drugs assessed in the abovementioned RCTs, but specifically, the different drug administration methods used to deliver the topic steroid inside the esophageal lumen, have been recognized as major reasons for the differences in the effectiveness of fluticasone propionate and budesonide in targeting EoE. A seminal paper demonstrated the importance of the vehicle used to release a topical corticosteroid into the esophagus by comparing, in a RCT, two formulations of budesonide (oral viscous and nebulized) given at the same doses [21]. 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 count reduction and endoscopic finding resolution. Since most of the trials assessing fluticasone propionate use inhalation devices to release the drug while budesonide was mainly provided through viscous solutions, the superiority of a drug over the other derives not from intrinsic anti-inflammatory properties but from success in targeting the esophageal mucosa [70]. Currently developing novel formulations of budesonide and fluticasone designed to provide an optimal coverage of the whole esophagus and remain in contact with the esophageal surface have proven much more effective than previous drug formulations. In this context and for adult EoE patients, two different budesonide formulations (effervescent tablets for orodispersible use and viscous suspension), with two different daily dosages for short-term treatment of EoE in adults, provided an efficacy of 100% in achieving histologic remission of the disease after only 2 weeks of treatment [66].

In contrast, evidence of the effectiveness of topic steroids to maintain remission of EoE over the long term is scant, with only one RCT finding low-dose budesonide to be more effective than placebo in maintaining EoE in histological and clinical remission in adults with EoE [114]. As for children, an extension of treatment in a RCT assessing high-dose fluticasone (1760 mcg/day) demonstrated a sustained remission in 73% of initial responders who then went to a 50% dose reduction when they were re-evaluated 3 months later [13]. A more recent prospective study in child responders (< 15 eosinophils/hpf) to swallowed fluticasone from metered dose inhalers revealed that long-term administration of the same doses maintained sustained remission in 59 and 63% of patients during months 13–24 and > 2 years of follow-up, respectively [4]. This data supports the recommendation of continuing with topical corticosteroids in those initially steroid–responsive patients to maintain remission.

With regard to safety issues, swallowed topical corticosteroids seem to have a favorable safety profile in the treatment of EoE, with no serious side effects reported. Among them, esophageal candidiasis, mostly incidental, has been described in up to 10% of patients of all ages, easily responding to specific treatment and with no need to withdraw steroid therapy. The possibility of suppressing systemic cortisol levels induced by topical steroid treatment has recently arisen, especially in children. Despite urine and/or serum cortisol levels not being suppressed in children [13] or adults [2, 66] in short-term RCTs, concerns over long-term effects of swallowed topical steroids on adrenal suppression in children are being provided by observational studies, including short series of EoE patients, with conflicting results due to different methods of determining adrenal function: basal cortisol levels, low-dose ACTH stimulation test, or standard dose ACTH stimulation test. Time of measuring cortisol levels after ACTH dose also varied among studies [1, 36, 38, 101]. While no differences in serum cortisol levels were found following treatment with swallowed fluticasone propionate (range 220–880 mcg daily) and budesonide (range 0.5–1 mg daily), with treatment lengths of 8–43 weeks [90], an additional study showed that adrenal suppression was present in 10% of children treated with swallowed glucocorticoids for at least 6 months and was found only in those treated with fluticasone propionate > 440 mcg daily [32]. No clinical sign of adrenal insufficiency

or growth impairment has been reported so far [4], but until more information is available, children with EoE should undergo cortisol monitoring to prevent adrenal insufficiency if they are receiving high doses of swallowed topical steroids for long periods, or concomitant use of inhaled/nasal corticosteroids for associated atopic diatheses [59].

Proton pump inhibitors: from diagnostic tools to therapeutic agents

The interaction between gastroesophageal reflux and EoE was assessed from the potential role that PPIs play in both conditions. It is a role which varies considerably from one set of guidelines to another. In the first descriptions of the disease [10, 28, 46], GERD and EoE were considered mutually exclusive disorders, and the first consensus guidelines for the diagnosis and management of EoE published in 2007 defined the disease either by normal esophageal acid exposure on pH monitoring or absence of response to PPI therapy [31]. In fact, these guidelines suggested that symptomatic patients with esophageal eosinophilia who responded to PPIs or had abnormal acid reflux suffered from GERD instead of EoE [85, 99]. Due to the a priori high likelihood of the coexistence of both conditions that affect young males, it was soon clear that this dichotomous consideration was counterintuitive. In 2011, the first prospective large series systematically evaluating PPI therapy in adult patients who had esophageal eosinophilia with EoE symptoms showed that up to 50% of patients responded to PPIs, with no differences found in clinical, endoscopic, and histologic features among the PPI responders and nonresponders, but with a considerable overlap between GERD (determined by pathologic esophageal pH monitoring) and EoE [72]. This study led to significant changes in subsequent 2011 EoE diagnostic guidelines [49], and esophageal pH monitoring was eliminated as a negative diagnostic criterion for EoE. Despite the mounting evidence that PPI responders had virtually the same clinical, endoscopic, histologic, and molecular features as EoE patients who did not respond to PPIs [30, 67, 75, 120, 122], a response to PPI therapy was considered sufficient to rule out EoE up to the evidence-based guidelines published in 2017 [59].

The first evidence on the ability of PPIs to achieve both clinical and histologic remission of EoE was provided in the pediatric literature [18, 85, 99], with preliminary research pointing to the symptomatic relief by PPIs also provided in this population [86]. The most extensive demonstration of the effectiveness of PPI therapy to induce clinical and histologic remission of EoE was provided by a prospective study carried out in multiple Spanish centers [35]: fifty-one children received treatment with esomeprazole 1 mg/kg per dose twice daily for 8 weeks. Post-treatment endoscopy demonstrated histologic response in 35 of them (68.6%), the peak being an eosinophil count below 5 cells per hpf in 24 children (47%) and between 6 and 14 in the remaining 11 (21.6%). Histologic response was achieved irrespectively of pH-monitoring results and type of EoE symptoms. Likewise, a recent meta-analysis of 33 studies on 619 patients with EoE (188 of them being children) reported an overall efficacy of 50.5% in histological remission and 60.8% in clinical response with the use of PPIs [57]. No differences were found between children and adults in terms of histological remission (54.1 vs. 49.6%, respectively) or clinical improvement (64.9 vs. 56.2%, respectively). Lansoprazole and rabeprazole showed the highest efficacies in inducing histologic disease remission (70.2 and 72.3%, respectively), compared with omeprazole and esomeprazole (53.5 and 46.8%, respectively). However, the limited number of studies using each PPI drug, their small sample size, and the heterogeneity among individual studies prevented finding significant differences. Finally, a nonstatistically significant trend toward a higher efficacy for achieving histologic remission was found when PPIs were given twice daily compared with once-daily dosages (55.9 vs. 49.7%, respectively).

In EoE patients with an initial response to PPI therapy, this drug should be used also to maintain disease into remission in the long term, because discontinuation of therapy leads to symptomatic and/or histological relapse. Despite the long-term therapeutic strategy and best maintenance doses for PPI therapy are yet to be defined, the most reasonable strategy at the moment is a progressive decrease in dosage to the lowest point that keeps the disease in remission [59]. The literature on maintenance of disease remission with PPIs, as for other therapies in EoE, is more limited. Until recently, the sustained efficacy of PPIs in children was limited to a short retrospective series comprising 11 patients with clinicopathological response to PPIs. In five children, a clinicopathologic response to PPIs was maintained in follow-up endoscopy [105]. Transient response to PPI therapy after an initial complete response has also been described, with recurrence of esophageal eosinophilia while still adhering to PPI therapy [26, 105]. However, the most solid evidence on the long-term effect of PPIs has been provided by a recent prospective multicenter study that has first shown that most PPI responder pediatric patients (78.6%) remained in clinicopathologic remission at 1-year follow-up on maintenance PPI standard doses (esomeprazole 1 mg/kg daily) [35]. These results are consistent with those obtained from adult series, which show that two thirds of patients maintained histological remission after at least 1 year of therapy with PPIs at standard doses [33, 76].

Long-term use of PPIs has been demonstrated to be safe in adults, with no significant side effects induced when taken at standard doses [11]. In contrast, and despite PPIs seeming to

be well tolerated during short-term use [118], no definitive data on long-term PPI safety in children is available [117].

Other investigational drugs in EoE

To date, only one 3-case series in adult patients demonstrated positive steroid-sparing effects of azathioprine or 6-mercaptopurin to induce and maintain long-term steroid-free remission [84] of esophageal eosinophilia, with no data having been provided for children. Several anti-allergic drugs failed to show a relevant impact on EoE-related symptoms or esophageal inflammation in pediatric EoE [48]. Montelukast, a leukotriene D4 receptor antagonist, used at standard doses in children [115] led to some symptomatic improvement in an open-label trial, with no patients achieving histologic response. Montelukast did not demonstrate superiority over placebo in maintaining remission in adult patients with EoE [3, 55].

Biologic agents have been intensely assessed in adult patients with EoE with most of them proving ineffective in achieving disease remission but with some degree of histological improvement. The anti-tumor necrosis factor α agent infliximab [112] produced no benefit in a small open-label series. The anti-interleukin (IL)-5 blocker mepolizumab was tested in RCTs involving children [8] and adults [113], while reslizumab was evaluated in children only [110], neither of them demonstrating significant differences between the active and placebo groups in terms of symptom relief nor histological remission. Similarly, the anti-IgE agent omalizumab showed no benefit in children according to an observational study [94] and neither in adults in a RCT [16]. Currently ongoing research with anti-IL13-based drugs in adults shows promising results that should be confirmed soon in children [59].

Endoscopic dilation in pediatric EoE

Esophageal strictures constitute one of the most severe complications of EoE that develop as a result of a long-standing untreated eosinophilic inflammation. Patient age and delayed diagnosis are recognized as determining factors for fibrotic esophageal strictures [24, 50, 102], and accordingly, they are found more commonly in adults than in children with EoE, likely due to the limited progression of the disease among the latter. However, narrow-caliber esophagi have also been repeatedly reported in pediatric EoE series [12, 64, 93], in which barium esophagrams demonstrate esophageal strictures in up to half of the cases that were unnoticed in endoscopy.

Similar to its use in other cases of rigid or fibrous esophageal strictures resulting from a prolonged esophageal inflammatory process, esophageal dilation with through-the-scope hydropneumatic balloons and Maloney or Savary bougies has constituted a treatment option for EoE patients from the earliest descriptions. A meta-analysis summarizing the information up to 2016 and overall including 27 studies on 845 individual patients (including 87 children) undergoing 1820 dilation procedures has been recently published [68]. Dysphagia improved in 95% of patients following dilation (95% CI 90–98%) with no effect on the underlying inflammatory process; thus, the duration of the effect disappears after 1 to 36 months. Therefore, repeated dilations are common in EoE patients in order to maintain dysphagia symptoms under control. Despite the limited information available for children, it should be concluded that dilation can be performed safely in children with fibrostricturing EoE with no more adverse events that in other causes of esophageal narrowing [65]. Finally, it is also advisable that esophageal dilation be used together with other diet or drug-based therapeutic modalities with anti-inflammatory efficacy in order to avoid complications derived from active eosinophilic inflammation of the organ [59].

Therapeutic algorithm for pediatric EoE: succeeding by just applying the evidence

The goals of EoE treatment in the pediatric population include resolution of symptoms, achieving and maintaining remission of the eosinophilic mucosal inflammation to prevent fibrotic esophageal complications, avoiding iatrogenic effects from drugs and nutritional deficiencies, and maintaining an adequate quality of life.

EoE is a chronic disease in which the esophageal inflammation progresses over time to esophageal fibrotic remodeling, leading to narrow-caliber esophagus and esophageal strictures. Making an analogy with therapeutic considerations on inflammatory bowel disease, all EoE patients should receive treatment targeted to resolve esophageal symptoms, cure esophageal inflammation (mucosal healing), and restore a proper esophageal caliber through endoscopic dilation in the case of fibrostenotic endoscopic findings [79]. No regulatory authority has approved specific medication to treat EoE yet, but solid data supporting all treatment categories have been published over the last decade, that support an evidence-based therapeutic algorithm (Fig. 1).

PPI therapy, topical steroids, and elimination diets have demonstrated effectiveness to induce and maintain histologic and clinical remission of EoE. No head-to-head comparative studies have been performed in order to define the order they should be used in patients with EoE, and therefore, all of them represent first-line therapies. Dietary therapy, once the culprit food has been identified, is less costly in the long run. However, it is more challenging to implement because it requires easy access to repeated endoscopy and sedation [14]. The election should preferably be done once discussed with the patient and their relatives and may depend on the age

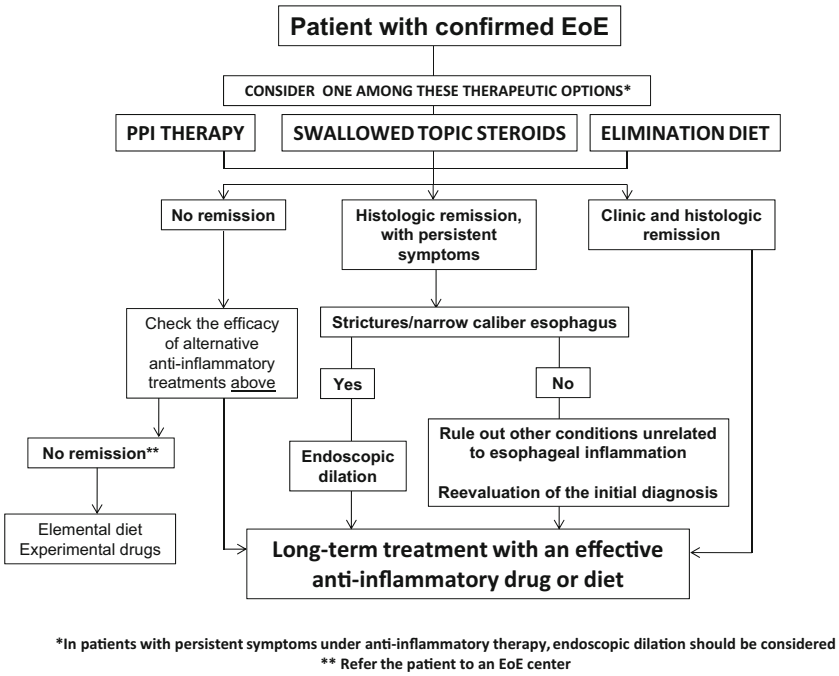

Fig. 1 Proposed therapeutic algorithm for eosinophilic esophagitis in clinical practice. * In patients with persistent symptoms under anti-inflammatory therapy, endoscopic dilation should be considered. ** Refer the patient to an EoE center

(adolescent and young adults might show poor adherence to diet), the severity of the disease (severe symptoms should be treated with topical steroid therapy), or the patient's and family's lifestyle and preferences or their ability to understand food label information [78]. Elimination diets should be considered with caution in children already on multiple dietary restrictions due to IgE-mediated food allergy, where a drug-based therapy is preferred.

The efficacy of any pharmacological/dietary therapy should be checked with a follow-up endoscopy after a 6- to 12-week initial course [49]. In addition, all patients with fibrostenotic abnormalities (including narrow-caliber esophagus and strictures) should be offered endoscopic dilation, preferably after a trial of medical/pharmacological therapy [69]. In case of failure in inducing histologic remission, checking the efficacy of alternative first-line measures is indicated [59].

It is well known that double dose PPI therapy leads to clinical and histological (< 15 eosinophils/hpf) remission in half of patients of all ages with suspected EoE [57]. Due to its safety profile, ease of administration, and high response rates, PPI therapy is considered a first-line treatment in adult patients with EoE and maybe also in children. However, the choice of therapy should be made after the patient and family are informed about the pros and cons of alternative therapies, such as diet and topical steroids. In case of clinicohistologic remission of the disease, most children will maintain long-term remission with PPIs given at standard doses [35].

Dietary therapy, although desirable for most patients, does not constitute a panacea because up to 10 and 30% will not respond to an elemental diet and a six-food elimination diet, respectively. Airborne allergens themselves or cross reactivity with food antigens may be responsible for refractoriness. Elemental diet is unfeasible in clinical practice and should be exclusively reserved for some refractory patients, and food allergy skin and blood testing-guided diet is discouraged due to limited efficacy and with conflicting results in the literature. In contrast, efficacy rates for empiric elimination diets are consistent between children and adults and should be preferred. Animal's milk, wheat/gluten-containing cereals, and eggs constitute the most common food triggers of EoE in patients of all ages from the USA, Spain, and Australia [78]. A step-up approach for empiric elimination diets might be cost-effective and improve patient uptake for dietary therapy. Therefore, a six-food elimination diet must be reserved for highly motivated patients unresponsive to a two- or four-food elimination diet [80]. All diets should be followed for a minimum of 6 weeks, after which their efficacy must be evaluated through symptoms and inflammation improvement in esophageal biopsies obtained during an endoscopic exam. Achieving clinicohistologic remission represents the baseline point, identifying specific food triggers in each particular patient through sequential food reintroduction. Foods should be individually reintroduced while continuing on the diet (one at a time) for a minimum of 6 weeks, with an endoscopic procedure after each individual food reintroduction. The final goal in a dietary therapy for EoE is to identify which food(s) triggers esophageal inflammation and which does not, in order to design an individualized diet for each patient for the long term, avoiding exclusively the causative foods. When available, dietary counseling should be considered for patients on elemental diet, six-food elimination diet, and patient responders to empiric diets with long-term avoidance of multiple food triggers [78].

Developing novel steroid formulas will solve the problem of the limitations of the current topical steroids, which are not designed for esophageal delivery. When available, oral viscous formulas should be preferred instead of metered inhaled devices, since the former provide significantly higher levels of esophageal contact time with the drug, which correlates with lower eosinophil counts [21]. Induction doses to achieve EoE remission in children are 880–1760 mcg/day for fluticasone propionate and 1–2 mg/day for budesonide. Maintenance doses might be half of this in most of the patients [59, 70]. The daily dose should be split to be administered in the morning after breakfast and at night before going to bed. Because the esophagus is a challenging target organ for topical drugs due to its peristaltic mobility, clearance of esophageal content accelerated by saliva and gastroesophageal reflux, and upright position most of the time, clear instructions should be given to patients and parents. Eating or drinking, rinsing the mouth, or brushing the teeth should be avoided at least 30 min after steroid administration to prevent the drug be washed down to the stomach.

Effective treatments for EoE might be interchangeable, seeing as two recent series have reported that patients responsive to diet/topical steroids may also achieve further remission on PPI therapy and vice versa [58, 108]. Once the therapy is instituted, the choice might be changed over time due to treatment side effects or the unwillingness of the patient to continue medication or dietary restrictions.

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. Although several authors have assessed the combination of drug and dietary-based therapies for EoE, especially in the pediatric literature [17, 45], it is a practice that is not supported by the best clinical evidence. When a patient achieves disease remission with PPIs or swallowed steroids, imposing dietary restrictions is unnecessary, as they generally add no benefit but have a negative impact on a patient's quality of life [45]. 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 maintaining it in the long term. Combining different therapeutic interventions in EoE usually leads to misleading and unreplicable results in the literature [71]. Skin testing-guided elimination diet is a prime example. The outstanding results (77%) published by Spergel et al. in 2002 [109] have not been replicated at any other centers to date. The main reason is likely to have been that overall efficacy was due to a combination of three different strategies (skin testing-guided elimination, elemental diet in those in which skin testing-guided diet was too restrictive, and empiric elimination of cow's milk). A combination of topical steroids with specific food elimination was proposed as superior to individual therapies [17], but patients already were in histological remission with either steroids or diets, making this unnecessary.

To conclude, PPIs, topical swallowed steroids, and dietary therapies based on empirical approaches have all proven to be effective treatment options for achieving and maintaining remission of EoE, and they should be offered to children with the disease. 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, healthcare facilities and resources, and the evolving circumstances of a chronic disease.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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