

Dietary Treatment for Children and Adults with Eosinophilic Esophagitis: Which Patient and Which Doctor Is It Suitable for?

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Keywords

Eosinophilic esophagitis · Food hypersensitivity · Diet therapy · Formulated food · Food elimination diet

Abstract

Background: The effectiveness of dietary therapy to induce remission of eosinophilic esophagitis (EoE) has been evaluated over the last decades and summarized in meta-analyses. Choosing the dietary modality, identifying the most suitable patients, and implementing specific prerequisites are essential to ensure long-term success. **Summary:** Impractical exclusive elemental diets provided the highest remission rates in EoE; however, they are not recommended due to their numerous disadvantages and detrimental effects on patient quality of life. Allergy testing-guided diets for EoE are limited; their insufficient effectiveness and low reproducibility are due to poor accuracy of skin or serum test results in identifying EoE food triggers. Initial experiences with a six-food elimination diet have provided evidence of high and predictive effectiveness rates and paved the way for less restrictive and more efficient step-up approaches, including four-food, two-food, and most recently, milk elimination diets. Dietary treatment for EoE is challenging for patients and families and requires certain skills to ensure success in the short and long term. **Key Messages:** The selection of appropriate pa-

tients is essential to ensure the success of and long-term adherence to dietary treatment of EoE. As normal triggers for EoE are commonly found in the staple diet, it is important to ensure adequate nutritional substitutes to avoid nutrient deficiency risks when long-lasting feeding difficulties or extensive restrictions are present. Specialized facilities in dietary therapy should adopt patient-centered and personalized approaches in order to provide timely monitoring and support for complex cases.

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Introduction

It has been 3 decades since Stephen Attwood and colleagues described, in 1993, a novel clinicopathological entity with esophageal eosinophilia and dysphagia, not caused by gastroesophageal reflux [1]. At the same time, Alexander Straumann et al. [2] described a 10-patient series with dysphagia, who presented with eosinophilic infiltration of the esophagus and endoscopic abnormalities. This entity was called *idiopathic eosinophilic esophagitis* (EoE), and Straumann warned that it would be increasingly frequent in the future. However, it still took a decade for the disease to increase sharply; since then, frequency has continued to grow almost to

epidemic proportions, from which we have gained an enormous amount of knowledge.

EoE is defined as a chronic immune-mediated inflammatory disease of the esophagus, characterized by symptoms of esophageal dysfunction and eosinophilic infiltration of this organ's mucosa, which cannot be explained by secondary causes [3, 4].

Since the first descriptions of the disease, EoE has been related to atopy: patients frequently present asthma, rhinitis, conjunctivitis, atopic dermatitis, IgE-mediated food allergies, and eosinophilia and high levels of total and allergen-specific IgE (sIgE) in blood analysis [5]. This presentation led to linking the disease with a Th2-mediated response [6]. The empirical demonstration of EoE as an allergic disease came in 1995, soon after EoE characterization, when it was shown that symptoms and pathophysiological features reversed after eliminating all food antigens from the diet [7]. The frequent environmental sensitization that patients with EoE present also led to the implication of aeroallergens in the origin of this disease. However, this hypothesis has been discarded over time [8], and the role of environmental antigens in EoE today are residual [9].

Dietary treatment represents a first-line therapy for EoE patients, together with proton pump inhibitors and topical corticosteroids [3]. The first diet or drug-based therapeutic interventions for EoE were tested in pediatric patients shortly after the characterization of the disease [10, 11], and over the last 2 decades, our knowledge about them and applicability in clinical practice has improved greatly. Among first-line therapeutic options for EoE, implementing a dietary approach is probably more complex than using anti-inflammatory drugs and requires a greater degree of involvement from patients and their families. However, dietary therapy is the only option directed at the primary cause of the disease and therefore capable of controlling symptoms and esophageal inflammation, without the need for drugs.

In this article, we will discuss diet therapy for EoE by providing the most up-to-date relevant information on the effectiveness of the different alternatives to achieve and maintain disease remission and on practical guidance to achieve the best results through diet in clinical practice.

Dietary Options to Induce Remission of EoE

Three different dietary approaches have been practiced in EoE patients, each aiming to minimize the effect of dietary allergens on the esophageal mucosa: an exclusive elemental formula diet; a diet based on a multimodality of

serum or skin allergy testing (or allergy test-directed food elimination); and “empiric” food elimination diets, based on avoiding the food groups most involved in triggering and maintaining EoE. The goal is to achieve disease remission and esophageal biopsy normalization and to identify the specific food antigen/s for each patient, through food reintroduction challenges. In the medium and long term, disease remission will lead to endoscopic normalization if there are no rigid fibrous strictures requiring dilation.

Exclusive Elemental Diets: The Most Effective Approach

An elemental diet is an amino acid-based artificial formula lacking all antigenic capacity [12]. Exclusively feeding with this formula has been used as a treatment option for EoE in children [7, 13], and, to a lesser extent, in adults [14, 15]. In 1995, Kelly and colleagues [7] published an investigation on 23 pediatric patients with dense esophageal eosinophilia and long-standing intractable esophageal, attributed to gastroesophageal reflux and unresponsive to standard medical therapies – some with a Nissen fundoplication. Of these, 17 patients underwent a dietary trial of exclusive feeding with an amino acid-based formula for a minimum of 6 weeks; 12 children completed the trial, and 10 had a follow-up endoscopy. Eight patients had symptom resolution, and two had improved symptoms. Furthermore, the peak eosinophil count decreased significantly after treatment, from a median of 41 to 0.5 in esophageal biopsies. Patients became symptomatic again after the specific foods were reintroduced [7]. The findings were later confirmed in the literature, and an elemental diet also proved highly effective in children and adolescent with EoE, who were nonresponsive to proton pump inhibitors. Symptoms resolved after only 8.5 days in almost all patients, while median esophageal eosinophil density decreased from 33.7 eosinophils per high-power field (eos/hpf) prior to intervention to 1.0 after the intervention [13]. However, these early works made clear the fact that one of the main limitations of the elemental diet in EoE patients was its poor palatability, requiring administration through a nasogastric tube in most patients [13, 16].

An exclusive elemental diet has been less used in adults with EoE, despite it inducing clinical and histological remission in most cases [14, 15]. Peterson et al. advised a group of 29 adults with active EoE to avoid any kind of food except an elemental formula for 4 weeks: 3 patients abandoned the study protocol on the very first day and eight more consumed forbidden solid foods during the study period. Among the 18 patients who completed the

protocol, all but one achieved histological improvement (≤ 10 eos/hpf or > 10 eos/hpf but $<$ half pretreatment eos/hpf), providing a per-protocol effectiveness of 94.4%; however, this reduced to 58.6% when data were expressed as intention-to treat based on 4 weeks of elemental diet. Participants in this study lost between 3 and 7 kg or more over the study period. Esophageal inflammation rapidly recurred in all patients after resuming a normal diet [14] within the first week. In order to overcome difficulties in diet adherence, Warners et al. provided physician and dietitian monitoring to 21 adults with active EoE recruited for a second study: all but 4 patients completed the study. Among the 17 who adhered to the elemental diet, 88% became completely asymptomatic; histological remission (defined as ≤ 15 eos/hpf) was achieved in 12 patients (71%), the remaining presenting eosinophil count reductions. Weight loss in 4 weeks was only 1.4 kg; patients experienced a decline in social life during the study period [15].

A meta-analysis that summarized results from 13 studies, including 429 EoE patients (411 children and 18 adults), provided an overall effectiveness for exclusive feeding with an elemental diet of 91% [17], making this option one of the most effective therapies for EoE, superior to almost any pharmacological alternative.

Limitations and Feasibility of Elemental Diets in Clinical Practice

Despite all of the above, there are several deterrents for prescribing this alternative in clinical practice. The disadvantages include poor adherence, low palatability, risk of weight loss, and high costs not always reimbursed by insurances [14, 15, 18]. Long-term avoidance of solid food in children under 2 years old, or with known feeding dysfunction, may lead to delayed oral-motor skill development [19]. In older children, adolescents, and adults, the negative impact of elemental diets on social activities, psychological well-being, and health-related quality of life represents an additional limitation [20]. Therefore, current guidelines give the elemental diet a limited role in treating EoE [3, 21].

There are a few clinical circumstances in which a potential role has been proposed for exclusive elemental diets for short periods of time. These include highly refractory infants and toddlers (among whom having no additional food may be better tolerated); bridge therapy while waiting for investigational drugs; patients who wish to remain in remission while investigating the casual role of unusual foods and aeroallergens on their disease [22]; not responding to an extended exclusion diet; or not eating solids [23]. These usages in very selected cases [24],

however, have not been investigated in real-world clinical practice.

Finally, elemental formulas have been added to other dietary alternatives, as an allergen-free supplement capable of guaranteeing adequate intake of nutrients and calories [25]. Despite the addition of amino acid-based formulas to elimination diets not providing further benefit in decreasing tissue eosinophilia, it did result in a significant improvement of HRQoL of patients [26].

Food Allergy Testing-Guided Diet

Once exclusive feeding with amino acid-based formulas, with complete absence of residual allergenicity, brought about the remission of EoE symptoms and the recovery of the esophageal mucosa, the prospect of an individualized dietary therapy led to elimination diet guided by allergy testing. Authors used the different allergy tests available, including skin prick testing (SPT), atopy patch testing (APT), and serum food-sIgE testing [27] to pursue targeting food etiology of the disease. In 2002, pioneering research by Spergel et al. [28] reported the results of a combination of SPT and APT to target potential EoE triggering foods in a series of 26 children: nineteen patients had a positive SPT; the most common foods identified were milk and egg (both 36%). Twenty-one patients also had a positive APT, and wheat and rye being the most common triggers. Patients were instructed to avoid all trigger foods for at least 6 weeks. Seven patients received elemental diet exclusive feeding due to multiple trigger foods. In clinical follow-up, 18 patients were asymptomatic, and eosinophil count decreased from 55.8 eos/hpf to 8.4 eos/hpf; 70% of patients resolved eosinophilic infiltration and 6 additionally had their eosinophilic count reduction [28]. These apparently promising results motivated many clinicians to perform allergy tests on EoE patients over the following decade, but without ever achieving the reported 70% efficacy. This effectiveness, however, was not a result of allergy testing. It was rather due to the addition of universal remission after feeding amino acid-based formula to those patients who tested positive for 5 or more foods, the real remission rate being only 49%. The same group of authors updated their results in 2012 and found normalization of esophageal biopsies with an allergy testing approach with APT/SPT in 53% of patients. This rate increased to 77% when patients empirically removed milk from their diets, in addition to food detected by allergy testing [29]. Notably, the inference of causality to a food as a trigger for EoE in these studies was not made by documenting the recurrence of the eosinophilic infiltrate through endoscopy and esophageal biopsies; it was made by

symptomatic recrudescence reported by parents after the food challenge. This makes the accuracy questionable, as we know that correlation between symptoms and biological activity in EoE is poor [30]. In fact, a low accuracy has been reported for allergy skin tests in identifying milk, and the most common culprit food linked to EoE in pediatric patients. The negative predictive value (NPV) of APT results for milk was as low as 31.4%; the NPV of SPT for milk was even lower (29.3%). Therefore, a negative test for milk on SPT or APT does not rule out milk as a trigger food [29, 31]. The NPV of the combination of both methods for milk is only 44% [29]. The same has been reported for cereals in adults with EoE: in a study involving 6 patients who were sensitized to wheat and rye, according to SPT results or IgE determination, only 1 patient showed improved symptoms following a 6-week elimination diet of wheat, rye, and barley, with no changes in endoscopy and histopathological examination of the esophagus before and after diet [32].

Allergy testing-guided diets in adult patient results were even poorer than in children: Molina-Infante et al. [33] performed a 6-week elimination diet based on SPT, prick-prick test, and atopy patch tests results: 10 out of 15 patients recruited were nonresponders. Also in adults, Philpott and colleagues evaluated five different modalities of allergy testing and compared results with those obtained by an empirical six-food elimination diet (SFED) and sequential food reintroduction: no test proved accurate in predicting culprit food triggers in a series of 56 adults with EoE [34].

The experience gained up to 2014 regarding allergy testing-directed food elimination was summarized in the first systematic review and meta-analysis [17]: an overall effectiveness of 45.5% for allergy testing-direct food elimination was found, with better results in children compared to adults (47.9 vs. 32.2%, respectively). This systematic review was recently updated and provided a very similar efficacy of 45.7% [35]. Both systematic reviews considered collectively the results of different allergic techniques and their combinations, despite the different approaches used in the studies. Variations in allergy testing methodology, allergens tested, ways used to confirm the culprit allergen, length of food challenge, and description of outcomes, all producing significant heterogeneity, have been pointed out in a recent systematic review [36].

In 2016, a position paper from the European Academy of Allergy, Asthma and Immunology stated that measuring serum IgE levels and/or SPT was not sufficient to identify foods that cause EoE and recommended against dietary advice exclusively based on IgE-mediated sensitization to

foods since it did not improve EoE in a significant number of patients [37]. Currently, no clinical practice guidelines recommend allergy tests to inform food restriction in EoE [21], as its utility is concordantly low [3].

Other alternative options were subsequently tried, but with low success. The most imaginative was esophageal prick testing (EPT) by challenging directly the esophageal mucosa with local injections of allergen extracts [38]. This was assessed in a pilot study of 8 adult EoE patients; 5 showed immediate mucosal blanching and/or total luminal obstruction after mucosal injection of soy ($n = 2$), banana, apple, oats, and hazelnut. Luminal obstruction improved after 10 min. Surprisingly, no patient experienced a reaction to milk, wheat, or egg injections, even though they are the most common EoE food triggers.

An increasing role for IgG4 has been recognized: after demonstration of massive IgG4 concentration, compared to controls, in the esophageal tissues of adult EoE patients with active disease, as well as increased food-specific serum IgG4 to the foods that are most associated with EoE, namely, milk, wheat, egg, and nuts [39]. Further studies confirmed these results [40–43] and found a correlation between tissue IgG4 levels and esophageal peak eosinophil count, severity of histological features, and Th2 cytokines gene expression levels [42]. In addition, elevated production of food-specific IgG4 was found throughout the upper gastrointestinal tract in EoE subjects [44]. While all these studies support a pathophysiological role for IgG4 in EoE, the ability of IgG4 testing to guide dietary elimination therapy also provided poor results [45].

Empiric Elimination Diet

Empirical elimination strategies consist of excluding from the patients' diet the foods most related to food allergies, without the need to perform skin or serological sensitization tests. This dietary approach strategy was the last to arrive in the EoE literature, despite it presenting the greatest development, both in clinical practice and in research, due to the high reproducibility of its results. As in any other dietary intervention, the goal is to achieve normalization of the esophageal mucosa, to identify, from there, the food or foods responsible for EoE through food challenge and histological monitoring of tolerance or reactivity against each reintroduced food.

The SFED as an Effective and Reproducible Option

In 2006, Kagalwalla et al. [46] compared an elemental diet with a SFED in children with EoE. Cow's milk protein, soy, egg, wheat, peanut/tree nut, and seafood

were excluded from patients' diets, as these were foods most commonly associated with IgE-mediated food allergies in American children [28, 47]. After a treatment length of 6 weeks and dietitian counseling, peak eosinophils count in esophageal mucosa decreased to ≤ 10 cells per hpf in 74% of patients; this result was not significantly different from the 88% rate obtained with an elemental diet in a comparative pediatric series [46]. To identify specific foods responsible for esophageal inflammation, those children who achieved histological remission after the SFED underwent sequential single-food reintroductions to discover specific foods or foods causing EoE. This was done by documenting recurrence of eosinophilic inflammation [48]. After at least 6 weeks from introducing a new food, patients underwent an endoscopy with esophageal biopsies; a dietitian supervised the reintroduction process [48]. Most common triggers were cow's milk (74%), followed by wheat (26%) and egg (17%). Although not every patient reintroduced all excluded foods under endoscopic monitoring, this approach required an average number of 5.6 endoscopies per patient [48].

Subsequently, the approach was simultaneously investigated in adults in two studies carried out in the USA and Spain [25, 49]: in the first, Gonsalves et al. [49] found that 74% of adults with EoE achieved ≤ 15 eos/hpf after 6 weeks of following a SFED, with 64% having ≤ 5 eos/hpf. Scores of dysphagia decreased in 95% of patients after a dietary approach. Reintroduction of one food group every 2 weeks was offered to patients who achieved ≤ 5 eos/hpf, and an upper endoscopy was performed after 4 weeks (after 2 food groups were reintroduced) or before in cases where patients became symptomatic. Symptom recurrence occurred with a median time of 3 days after exposure to trigger foods. The most common culprit foods were wheat (60%) and milk (50%); 15% of patients had more than one trigger identified. No patient had seafood as a trigger. SPT results did not predict food triggers accurately [49]. A decrease in social activity was noted in male patients and a decrease in emotion was noted in male and female patients participating in this study.

In Spain, Lucendo and colleagues reported a 73.1% histological remission (< 15 eos/hpf) in adult patients with EoE who underwent a modified SFED for 6 weeks (which included all cereals, milk, eggs, fish/seafood, legumes/soy, and peanuts) [25]. In responders, all excluded foods were reintroduced singularly, with upper endoscopy with biopsies performed to identify food triggers after 6 weeks of regular intake of all previously excluded food: cow's milk was the most common trigger (61.9%), followed by wheat (28.6%), egg (26.2%), and legumes (23.8%) [25].

One out of 3 patients had a single offending food, another third had two food triggers, and the remaining had three or more foods identified. Adherence to the diet maintained EoE remission for up to 3 years.

A meta-analysis, summarizing results up to 2014 from seven studies comprising 197 patients (75 children and 122 adults) undergoing a SFED diet, provided an extremely homogenous effectiveness of 72.1% (95% CI: 65.8–78.1%) histological remission rate [17], similar to that reported for some topical corticosteroids [50]. A more recent meta-analysis including 701 patients showed that SFED has a 61.3% (95% CI: 53.0–69.3%) efficacy [35].

The potential role of pollen and other aeroallergens has been a much discussed topic in EoE. Although growing evidence increasingly calls into question the possibility that they constitute a relevant trigger [8], they may be implicated in a minority of cases. A single study has reported a reduced effectiveness of a SFED during pollen season, as well as lower response to the diet among EoE patients sensitized to pollen compared to those without sensitization [51].

Limitations of the SFED derive from difficulties in implementation due to its complexity and cost from the need to consume unprocessed foods [52]. A recently published meta-analysis documented that the effectiveness of a SFED increased in patients who were offered amino acid-based formulas to supplement dietary restrictions compared to those who were not (the histological response rate being 79.4 versus 56.3%, respectively [35]). Although not specifically analyzed, the SFED has been accused of reducing the quality of life of patients who follow it, due to the extensive restrictions in social activities it imposes. The need for numerous and frequent upper endoscopies to find the food or foods responsible for EoE in each patient is a further deterrent.

The SFED is today a treatment alternative that is no longer recommended. Instead, the essential role it played in identifying the foods responsible for EoE is recognized as leading the way for the design of simpler empirical elimination schemes. Milk and gluten, followed by eggs and legumes/soy, were the major food triggers in the vast majority of patient responders to SFED, while fish, seafood, and nuts were in a minority [25]; therefore, simpler and more convenient empirical elimination diets could be implemented.

The 4-Food Elimination Diet

In a prospective multicenter study carried out in Spain, Molina-Infante et al. found that 54% of adult patients with EoE were able to achieve histological remission after

6 weeks of a 4-food elimination diet (FFED), which excluded all dairy products (including cow's, goat's and sheep's milk), gluten-containing grains, eggs, and legumes (namely, lentils, chickpeas, peas, beans, peanuts, and soya) [53]. In addition, 31% of the patients who failed to reach histological remission with a FFED diet did so after increasing food restriction to a SFED. Notably, no seasonal differences were noted in remission rates.

In children, a FFED that excluded cow's milk, wheat, egg and soy induced histological remission in 64% of patients after 8 weeks [54]; one single food trigger was identified in 62% of patients, with cow's milk being the most common in triggering esophageal inflammation after food challenge. The pollen season did not influence the responses in this cohort. A recent meta-analysis of 8 studies, which summarized the effectiveness of a FFED in 302 active EoE patients of all ages, found it induced remission in 49.4% (95% CI, 32.5–66.3%) of patients, with a significant inconsistency in results [35].

A Step-Up Approach: The 2-4-6 Elimination Diet

A multicenter study carried out in Spain and Italy and involving adult and pediatric patients with EoE was innovative in its dietary approach, reserving the concept of extensive food restriction for non-responding patients exclusively. A step-up approach, commencing with a two-food elimination diet (TFED), was proposed, following demonstrations that milk and wheat/gluten were the most common food triggers of EoE in repeated studies. After 6 weeks, 43% of patients achieved clinical and histological remission, irrespective of age. A FFED was then offered to nonresponders, with a SFED reserved as the final rescue therapy for motivated patients who failed the previous two alternatives [55]. Milk was the culprit food for 81% of patients, and most responders to either a TFED or FFED presented 1 or 2 food culprits. The authors demonstrated this step-up approach was able to reduce the number of endoscopic procedures compared to initial SFED, shorten study time, and avoid unnecessary dietary restrictions [55]. In addition, starting with a TFED reduced dietary costs compared to a SFED and improved adherence [56]. Unfortunately, to date, no additional study has tried to reproduce these results.

One-Food Elimination Diet

Milk and dairy products have been repeatedly demonstrated as the most common triggers of EoE in patients of all ages [57]; therefore, it was clear that the next step in the dietetic approach was a milk-free diet. Among the potential advantages of this approach was the need for only one upper endoscopy after the elimination of milk to

demonstrate its involvement in EoE. According to a recent systematic review, avoiding cow's milk was able to induce clinical and histological remission in 51.4% of patients, with most research on a one-food elimination diet having been developed in children [58–63].

A milk-free diet is much more bearable for the patient and their family than the more extensive restrictions imposed by the SFED and FFED. However, although avoiding milk removes eosinophilic inflammation and derived symptoms without the need for any medication, its ubiquity in processed foods continues to be a challenge in the daily lives of some patients.

The one-food elimination diet has been assessed in randomized control trials: recently, a randomized trial compared a one-food elimination diet (animal milk including cow, sheep, and goat milk products) to a SFED (animal milk, egg, wheat, soy, fish and shellfish, and peanut and tree nut elimination) in adults with EoE, for 6 weeks. In this research, 34% of adults reached histological remission (<15 eos/hpf) after animal milk elimination and 40% with a SFED [64], this difference not being statistically significant. Some patients without histological response after one-food elimination diet underwent a SFED, but only 43% achieved remission. The poor control of proper adherence to this diet might explain unexpectedly low response rates to SFED in this trial.

It has long been known that the vast majority of patients with EoE triggered by dairy proteins were able to tolerate an extensively hydrolyzed whey formula [65], but this alternative helps little in the daily lives of patients. Experiences in patients with IgE-mediated allergy to cow's milk proteins showed that a portion of patients could tolerate heat-denatured milk proteins [66]. In 2013, a retrospective case series documented 3 out of 4 pediatric and adolescent patients with cow's milk-mediated EoE were able to tolerate baked milk [67], and later a flexible approach to cow's milk elimination (which allowed cookies and baked products with milk traces) was not significantly worse than strict adherence in terms of disease remission [60]. Long-term strict avoidance of food in EoE patients could determine a greater risk of anaphylaxis if the food is reintroduced, as already reported with a cow's milk elimination diet [68, 69]. As such, a more flexible trial with food elimination can be tried in patients with histological remission.

Despite selection bias and small sample size bias possibly affecting results of previous research, the option to modify milk allergenicity by heat processing deserved to be investigated. Thus, a further prospective study, carried out on 18 adult and adolescent patients with EoE triggered by milk, demonstrated that three quarters of

Table 1. Diet strategies available for treating pediatric and adult EoE patients, along with efficacy and some considerations for clinical practice

Diet therapy	Effectiveness (<15 eos/hpf)		Considerations
	in children (%)	in adults (%)	
Elemental diet	~90	71–94 ^a	Low palatability, poor adherence, frequent need of nasogastric tube, impairs psychosocial functioning and quality of life, weight loss
Allergy testing-directed food restriction	~53	~32–34	Consistent low efficacy in adult studies and conflicting results in pediatric studies. Limited accuracy of test for most common food triggers in EoE. Methodological issues in some studies (response defined by symptoms, not by histological reassessment)
Six-food empirical elimination diet	~60	Variable results, 40–71 ^b	Many endoscopies required, adherence considerations, highly restrictive. Numerous endoscopic procedures after documenting response. Impairs psychosocial domains and quality of life
Four-food elimination diet	56.3	~38–54	Less restrictive than 6FED
Two-food elimination diet	40	43	Single study requiring external validation. All patients were found to have 1 or 2 food triggers, which makes them best candidates for maintenance therapy
One-food elimination diet (milk avoidance)	~55	34	Apart from cow’s milk, sheep’s and goat’s milk are restricted due to cross-reactivity

eos/HPF, eosinophils per high-power field. ^a94% histological improvement (≤ 10 eos/hpf or > 10 eos/hpf but $<$ half pretreatment eos/hpf) based on Peterson et al. [14]. ^bRecent RCT with 40% efficacy [64] first meta-analysis with 71.3% efficacy [17].

them tolerated sterilized cow’s milk (specifically, subjected to temperatures over 100° for 20 min instead of ultra-high temperature processed), with no recurrence of eosinophilic inflammation or symptoms [70]. In Table 1, efficacy of different dietary therapies is summarized.

Long-Term Efficacy of Dietary Therapy in EoE

As EoE is a chronic disease in which inflammation and symptoms recur after treatment discontinuation, long-term maintenance therapy is usually recommended to retain remission and avoid potential complications. Once food groups responsible for EoE have been identified, after the reintroduction phase with empirical elimination diets, long-term avoidance of triggering foods is recommended. Unlike the extensive literature on remission induction diets, only a handful of small series have assessed the ability of patients, who remain compliant with avoiding known dietary triggers, to maintain full sustained remission long term.

First reports on long-term effectiveness of dietary therapy came from Kagalwalla et al. [48]: after responding to a SFED and having food triggers identified by sequential food reintroduction, EoE was maintained in remission in five diet-adherent children, without treatment-related complications

or growth deceleration, after a follow-up of up to 4 years. A recent study of children with EoE, treated with an elimination diet for almost 5 years, found that most attained histological remission with fewer side effects than patients treated with swallowed topical steroids [71].

After 3 years of follow-up, adults who continued to avoid culprit food(s) following SFED and single-food reintroduction maintained histopathological and clinical remission without drug treatment and even occasional dietary transgressions [25]. Among 21 adult patients who achieved histological remission, around 50% remained adherent and continued with symptomatic, endoscopic, and histological EoE features under control after a mean period of approximately 2 years. Loss of response in the remaining patients was mainly due to poor compliance with diet [72]. Finally, another study found that around 57% of patients who completed a SFED with identification of culprit food still were able to maintain the diet after an average period of 39 months [73].

However, the same studies also revealed the difficulties of long-term adherence and the frequent recurrence of EoE in a significant proportion of patients. Factors impacting adherence to diet therapy included treatment effectiveness, social limitations, and diet-related anxiety [73].

Nutritional Aspects of Dietary Treatment in EoE

Feeding difficulties are common in patients with active EoE, due to dysphagia, regurgitation, or recurrent vomiting. Food avoidance or compensatory behaviors to cope with symptoms include slow eating, cutting food into tiny pieces, and taking sips of water frequently [12]. Diagnostic delay may also increase the risk of strictures and complications, which worsen eating difficulties. Children with EoE may eat less than the recommended intake of some micronutrients such as vitamin D and calcium [74]. Therefore, appropriate selection of candidates for dietary intervention is mandatory, while nutritional monitoring and appropriate dietary counseling are of particular importance in at-risk individuals, including children with IgE-mediated food allergies who avoid more than 3 food groups [75].

Weight and body mass index can reduce slightly after starting an empirical elimination diet, but they do increase from baseline after completing food reintroduction. This has been seen in mean weight of children after a FFED [54], and similar results were shown after a SFED, in which the nutritional status of children did not worsen after 2 months of dietary therapy [76]. Nevertheless, regular assessment of macro and micronutrient intake is advisable in patients of all ages treated with elimination diets [75, 77], and appropriate substitution with permitted food or supplements can be recommended to achieve dietary requirements [78]. The involvement of a trained dietitian for counseling regarding replacement is advisable to ensure nutritional goals and to improve dietary adherence [78, 79]. They can also evaluate weight changes and provide guidance to help prevent social withdrawal as a result of an elimination diets [78].

In the long term, dietary therapy is generally safe, as patients usually only restrict one of two foods exclusively. However, some concerns have arisen in the literature regarding the effect of elimination diets on anthropometric profiles and growth, especially in children with EoE [54, 80]. Studies carried out in children with persistent IgE-mediated cow's milk allergy have shown increased risk of not reaching growth potential in adulthood [81, 82]. Finally, clinicians should be aware of the apparition of avoidant/restrictive food intake disorder, already reported in pediatric and adult patients with EoE [83, 84].

Barriers for Setting up Dietary Therapy for EoE

Dietary treatment is an attractive option for patients who may be concerned about being on long-term medication and are afraid of side effects. Before involv-

ing a patient in dietary treatment, we must acknowledge that it is not a panacea, and despite full adherence, a proportion of patients will never respond. Lack of adherence is a common problem, especially in adolescents and adults. In order to avoid wasted effort and resources on the part of the patient, they must be made aware of potential short and long-term barriers to implementation, and consent from the patients and/or their parents should be gained to show their understanding and agreement to participate [85]. Despite diet therapy being patient-centered, many on a therapeutic diet feel distress over food cross-contamination and the impact EoE can have on diet and social life [86]. Some barriers for dietary therapy are summarized below (Fig. 1):

- a) Presenting additional food restrictions unrelated to EoE. IgE-mediated food allergies are common in EoE patients, and they can also suffer from celiac disease or other food intolerance. In these cases, EoE usually will not be caused by the foods patients usually avoid [87], therefore additional food restrictions to treat EoE have to be added to the former, making adherence more difficult and potentially impairing HRQoL.
- b) Willingness to undergo repeated endoscopies with biopsies, which are essential in a food challenge protocol [88]. Sedation should be provided for all endoscopic procedures, and flexibility in scheduling endoscopic appointments depending on the histological results will facilitate patients' involvement in food reintroduction protocols [18].
- c) Patient lifestyle, occupation, and family habits will also determine suitability for dietary therapy, as the restrictions imposed by strict adherence to elimination diets make it impossible to consume highly processed foods or eat out, especially during the initial phases. Patients must ensure that they can eat at home or take prepared food to work or school, in order to guarantee a proper adherence to the diet. Resources and time needed to buy unprocessed food stuffs and cooking them at home should be also considered [78]. Adherence to diet undoubtedly diminishes in patients who travel a lot through work and/or may have meetings that revolve around food [73].
- d) The timing of when to start an elimination diet must also be considered, in order to try and avoid as much as possible scheduled food-related social events; it goes without saying that these should be restricted during the study period of an empirical elimination diet.
- e) The need to purchase predominantly unprocessed foods free of milk, gluten, eggs, or soy entails additional expenses and may not be readily available. It

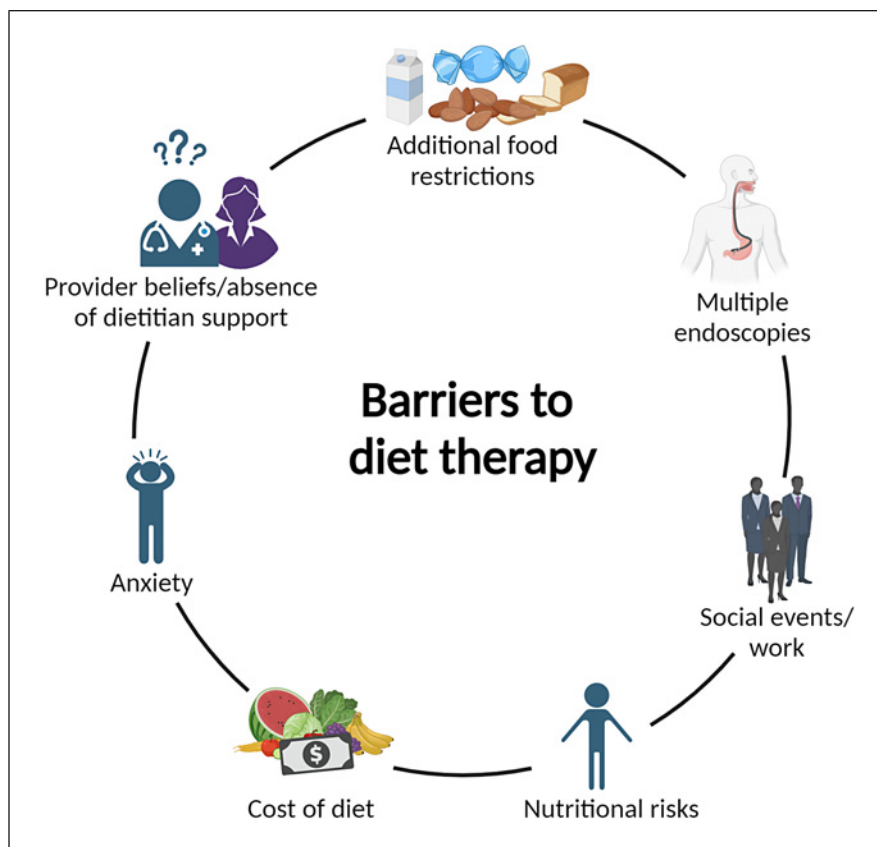


Fig. 1. Barriers to diet therapy. The details and description of each barrier are given in the text. Created with BioRender.com.

has been estimated that a SFED resulted in a 17.4% weekly cost increase compared to a regular diet in the USA [52].

- f) Due to potential nutritional risk and deficiencies, providing nutritionist resources has been proposed as essential when implementing dietary therapy for EoE [77, 78], especially in the youngest patients. However, older children, adolescents, and adults with EoE usually develop coping strategies to maintain proper nutritional status, and macro or micronutrient deficiencies are rarely found in these patient groups [74, 76]. Although absence of dietitian support may make it challenging to begin EoE dietary therapy [89], providing written practical advice to patients or families, such as reading food labeling, lists of ingredient, and recommended samples menus, has been shown to be effective in ensuring dietary adherence and proper nutritional intake in adults and adolescents [25, 53–55, 90].
- g) Long-term barriers to elimination diets include social situations that create challenges in following the diet. Anxiety related to elimination diet has been described to be higher in patients who stop adhering to it [73].

A survey of providers (including gastroenterologists and allergists) found that the most significant barrier to diet therapy in EoE was the belief that patients were not interested in and were unlikely to accept or adhere to diet therapy (58%); this was followed by concerns regarding multiple endoscopies during food reintroduction [89]. Although some healthcare providers viewed diet as the least effective treatment [89], most patients would recommend elimination diet therapy to others [73]. Furthermore, many patients preferred changing their diet to chronic drug therapy, viewing it as a more permanent solution [91]. Barriers to diet therapy in EoE are summarized in Figure 1.

Which Patients Are Best Candidates for Dietary Therapy?

Dietary treatment for EoE is not without difficulties for the patient and their family. Even when effective, we have already described that maintaining long-term adherence is challenging, and after 1 year, only half of patients are able to maintain dietary adherence. This results in disease recurrence and a switch to drug therapy. Therefore, clinicians

should explain the pros and cons of each therapeutic option and what is realistically attainable after therapy, both in induction or remission and in its long-term maintenance.

The most relevant advantage of diet therapy, and its main attractiveness for patients, is that it might identify the food or foods that trigger and maintain the disease. Food triggers for EoE do not change over time, so patients will be able to have some control on disease remission [79] and, in case of disease recurrence, to recover it by improving adherence. As already described in many chronic diseases, once patients feel better, adherence to treatment plans usually decreases. In the case of EoE, long-term adherence to diet and to clinical monitoring could be improved, as patients frequently do not return for clinical follow-up within the recommended time, even when symptoms such as difficulty in swallowing or compensatory eating behaviors reappear [92]. This is not exclusive to dietary treatment according to recent Dutch research, which showed at least 1 third of adult patients declared nonadherence to EoE therapy. The study showed a tendency for better adherence to diet compared to drug therapy (64.9 and 58.2% declaring proper adherence, respectively, although the difference is not statistically significant). Risk factors associated with poor adherence include age <40 years, longer disease duration, low necessity beliefs, and severe symptoms [93], with the latter most likely being a result of low adherence.

Concerns relating to the potential side effects of drug therapy when used long term have been shown to be a reason for dietary therapy in EoE: Iglesia et al. [94] reported a series of patients with PPI-responsive EoE who decided to stop medication and undergo a food elimination diet: two-thirds achieved histological response (<15 eos/hpf) after 6–8 weeks.

Best candidates for diet therapy are motivated patients, willing to accept repeated endoscopies, especially if more than a TFED is implemented, and who can manage the social limitations imposed by the diet [12]. (Multiple endoscopies may mean frequent workplace or school absenteeism). Other candidates are patients who prefer a more “natural” approach than medication.

When available, it is preferable that patients who chose diet therapy: receive counseling from a trained dietitian in order to avoid nutritional deficits; and to learn how to read nutritional labels and ingredient contents [95]; and be trained on how to prevent cross-contamination.

Requirements to Succeed with Dietary Therapy for EoE

Initially tested in a limited number of sites, dietary treatment of EoE has become more widespread over the years, due to the attraction of treating a chronic disease

without the need for drugs, and the limited effectiveness of most currently available pharmacological therapies [96]. However, a recent survey carried out in the USA on adult and pediatric gastroenterologists and allergists revealed that physicians prefer medication, viewing diet as the least effective treatment. Their belief that patients are disinterested and unlikely to adhere was identified as the greatest barrier for dietary therapy, followed by limited access to dietitians [89].

The widespread use of dietary therapy has also been accompanied by a reduction in its reported effectiveness; thus, the summarized efficacy of SFED in a first meta-analysis in 2014, on 197 patients in 7 studies, was 72.1% (95% CI, 65.8–78.1%) [17], but only 61.3% (95% CI, 53–69.3%) in a recent update on 701 patients from 17 studies [35]. Interestingly, the efficacy of the empirical SFED (the most restrictive but most effective dietary treatment of EoE) was not significantly better than milk elimination alone, in a recent multicenter clinical trial in EoE [64]. These data suggest that the success of a dietary approach for EoE depends, to some extent, on the site where this treatment is developed, and this deserves specific consideration. Consequently, both physicians and healthcare facilities should meet certain requirements to successfully treat patients with EoE using dietary therapy (Fig. 2):

- a) Doctor’s experience and specialization: specific experience and knowledge in the management and treatment of EoE is mandatory; ideally, a gastroenterologist or allergist who specializes in esophageal diseases and food allergies is advisable.
- b) Accurate evaluation of EoE and concomitant conditions, especially regarding additional IgE-mediated food allergies or food intolerances: knowing the patients’ lifestyle and their commitment to self-care and interest in the disease are also important points.
- c) Personalized diet therapy design: providers should be able to design a personalized dietary treatment plan for each patient, based on patient and family preferences and resources. Once a food trigger is identified, planning for long-term avoidance and possible replacement foods requires concerted effort.
- d) Multidisciplinary team: having a multidisciplinary team that includes food allergy dietitians and gastroenterologists to collaborate in planning and monitoring dietary therapy is advisable, especially when implementing the most restrictive diets.
- e) Patient education and orientation: the healthcare facility should provide appropriate patient education about the disease, the goals of dietary therapy, and necessary dietary modifications. Food label reading to

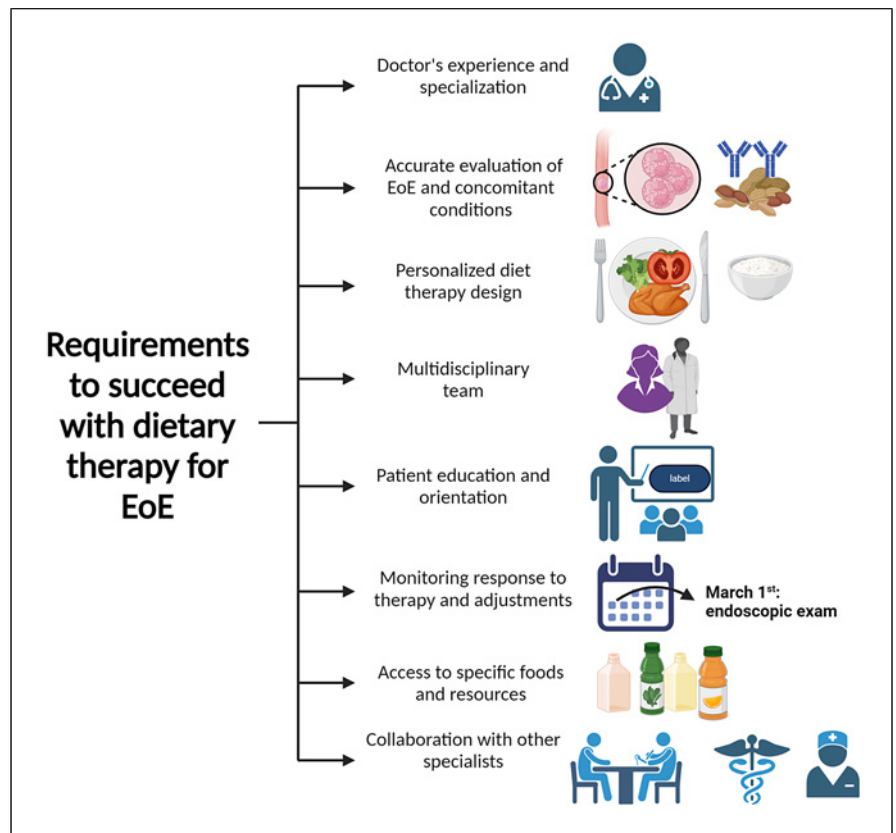


Fig. 2. Some requirements to succeed with dietary therapy in patients with EoE. Created with BioRender.com.

identify allergens is required but frequently complex, despite labeling laws mandating full disclosure of the priority allergen on food product labels. The 6 most common allergens associated with EoE are priority allergens in many countries, but sometimes they are defined under ambiguous terms, such as “starch,” “whey,” or “animal protein.” Special mention should be made regarding novel food ingredients, which are used to replace some potential allergens in processed foods. Providing patients and/or families with educational material and resources to help them understand and adhere to the dietary plan is recommended.

f) **Monitoring response to therapy and adjustments:** a facility willing to perform dietary therapy for EoE should ensure that endoscopic exams monitoring response to initial therapy and those to check food tolerance or reactivity are scheduled at appropriate times, usually every 6 weeks. It should also be flexible with appointments to allow for patient’s presentation of obvious symptoms after a food challenge. To increase the chances of success with dietary therapy, regular follow-up visits should be

scheduled to evaluate progress, perform control tests, and adapt the diet according to the patient’s progress.

- g) **Access to specific foods and resources:** doctors and facilities dealing with dietary therapy for EoE should have access to specialized foods and resources for patients on extensive dietary restrictions, to facilitate the effective implementation of dietary therapy. It has been shown that adding an amino acid supplement to provide extra nutrients and calories to patients under SFED increased histological remission rates to 79.4% (95% CI, 62.3–92.7%), compared with 56.3% (95% CI, 48.1–64.2%) when SFED was not supplemented [35].
- h) **Collaboration with other specialists:** to involve other specialists, such as allergists, nutritionists, psychologists, and other health professionals, to address specific aspects of the disease, fast tracking in special situations may prevent abandonment of dietary therapy and facilitate adaptation to food restrictions.

It is essential that the dietary treatment approach be patient-centered and holistic [12], through consideration of both medical and psychosocial aspects.

Which Diet Should We Recommend as First Line?

Today, a single-food elimination diet (i.e., animal milk) should be considered as the most suitable first-line approach in a pediatric patient with EoE, while adolescent and adults could obtain more benefit from a TFED. In case of non-response, a step-up empirical approach, up to FFED, can be considered. The vast majority of responsive patients will have only one or two independent food triggers for EoE, detectable after a reduced number of endoscopies. We do not recommend a SFED, either as the first choice for remission induction, or as the final stage of a stepwise approach.

We also do not recommend allergy testing-directed food elimination. The expected effectiveness has been shown to be consistently low, especially in adults [35], along with the risk of presenting multiple sensitization with negligible precision in defining potential dietary causes of EoE.

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