

## Dietary therapy for eosinophilic esophagitis: chances and limitations in the clinical practice

Alfredo J Lucendo & Javier Molina-Infante

To cite this article: Alfredo J Lucendo & Javier Molina-Infante (2020) Dietary therapy for eosinophilic esophagitis: chances and limitations in the clinical practice, Expert Review of Gastroenterology & Hepatology, 14:10, 941-952, DOI: [10.1080/17474124.2020.1791084](https://doi.org/10.1080/17474124.2020.1791084)

To link to this article: <https://doi.org/10.1080/17474124.2020.1791084>



Published online: 07 Jul 2020.



Submit your article to this journal [↗](#)



Article views: 88



View related articles [↗](#)



View Crossmark data [↗](#)



Citing articles: 2 View citing articles [↗](#)

REVIEW



# Dietary therapy for eosinophilic esophagitis: chances and limitations in the clinical practice

Alfredo J Lucendo <sup>a,b,c</sup> and Javier Molina-Infante <sup>b,d</sup>

<sup>a</sup>Department of Gastroenterology, Hospital General de Tomelloso, Tomelloso, Spain; <sup>b</sup>Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain; <sup>c</sup>Instituto de Investigación Sanitaria La Princesa, Madrid, Spain; <sup>d</sup>Department of Gastroenterology, Hospital Universitario de Cáceres, Cáceres, Spain

## ABSTRACT

**Introduction:** Eosinophilic esophagitis (EoE) is a non-Immunoglobulin E-mediated food allergy that currently represents the main cause of dysphagia and food impaction in children and young adults. Diet remains the only therapy targeting the cause of the disease. Relevant advances in recent years allow novel approaches to dietary therapy in EoE.

**Areas covered:** An up-to-date review on dietary therapy for EoE is provided, as a potential first-line anti-inflammatory therapy able to induce and maintain remission in a significant proportion of patients. Unpractical elemental diets and suboptimal food allergy testing-directed food restrictions paved the way for empiric elimination diets, which currently are to be considered as the most effective drug-free treatment for EoE. After largely restrictive empiric six-food elimination diets, most efficient step-up approaches now include four-food and two-food elimination diets. The potential of milk-elimination is also discussed.

**Expert commentary:** An empiric elimination diet step-up strategy should be currently considered as the initial approach for dietary treatment in EoE patients of all ages. Compared to a top-down strategy, step-up diets reduce the need for endoscopic procedures, shorten diagnostic process times, and avoid unnecessary restrictions. Furthermore, early identification of responders with few food triggers may select best candidates for maintenance dietary therapy.

## ARTICLE HISTORY

Received 22 March 2020  
Accepted 30 June 2020

## KEYWORDS

Eosinophilic esophagitis (EoE); food hypersensitivity; diet therapy; formulated food; food-elimination diet

## 1. Introduction

Eosinophilic esophagitis (EoE) is a chronic, antigen-driven inflammatory disease clinically presenting with symptoms of esophageal dysfunction and histologically characterized by a dense eosinophilic infiltration, defined by at least 15 eosinophils per high-power field (eos/hpf) restricted to the esophageal mucosa [1]. Initially characterized less than three decades ago as a distinctive esophageal disorder different from eosinophilic gastroenteritis, cases of EoE from all continents have been reported. However, its prevalence in Europe and North America has sharply increased, currently representing the main cause of dysphagia and food impaction in children and young adults [2]. Left untreated, the natural history of EoE consists of persistent esophageal inflammation and symptoms, which progress to esophageal remodeling with stricture formation and functional damage in the long term [3]. Consequently, EoE negatively impacts on the health-related quality of life (HRQoL) of patients by causing emotional distress and restricting social activities [4]. The chronic and progressive nature of EoE indicates a need for treatment aimed to reduce symptoms and to normalize esophageal histology and endoscopic appearance, with treatment cessation usually leading to clinical and histopathologic relapse [5].

From the earliest descriptions of the disease, EoE is recognized as a particular form of food allergy: In 1995, 10 children with persistent dense esophageal eosinophilia, theoretically attributed to gastroesophageal reflux disease refractory to antacids, antisecretory drugs and fundoplication, were successfully treated with an amino acid-based formula (elemental diet) for 2 months. Eight patients showed total resolution and the other two exhibited improvement of symptoms in parallel with an average reduction of eosinophil peak counts from 41 to 0.5 eos/hpf [6]. This study clearly established that the esophagus behaves as an immunologically active organ, capable of developing an allergic inflammation due to loss of tolerance to harmless antigens [7] and established for the first time dietary treatment as an effective option for the management of these patients, before other drug-based treatment alternatives were proposed. However, difficulties in implementing a well-tolerated and effective dietary approach in a high proportion of patients slowed down research on dietary therapy for EoE for almost a decade, in which corticosteroid-based treatments appeared first [8,9], and proton pump inhibitors (PPIs) later [10] as prominent therapies for EoE.

Empiric elimination diets for EoE represented a new approach [11] that gave prominence to dietary therapy as an effective and feasible drug-free alternative, attractive for many patients [12]. Currently, dietary therapy is included in the

**Article highlights**

- EoE is triggered mainly, but not exclusively, by food antigens. Unlike pharmacological therapy, dietary therapy is the only treatment that targets the primary cause of EoE and not the inflammatory consequences of the disease.
- None of the available food allergy testing, either in skin or blood, can adequately predict the causative foods triggering EoE. IgE-based food allergy testing is not recommended to design dietary therapy in patients with EoE.
- Empiric six-food elimination diet (SFED) has been key to identify the causative foods that trigger EoE, with cow's milk, wheat/gluten, eggs and legumes/soy consistently reported to be the most common food triggers in Europe, United States and Australia. However, the high level of restriction and large number of endoscopies that a SFED requires, currently discourage its use as initial therapy for EoE.
- A step-up empiric elimination diet currently represents the initial dietary approach for EoE. In children a milk elimination diet should be considered as the initial approach, whereas adult patients may initially be treated with a two-food elimination diet.
- Generalizing the use of dietary therapy for EoE requires providing patients with clear instructions on foods to avoid and how to substitute them. Physicians should also be provided with homogeneous schemes for food elimination and reintroduction, cross-reactivity and lengths of initial treatment and food challenges before endoscopies, preferably based on objective quality data.

therapeutic algorithm of EoE as a first-line treatment for children and adults, along with swallowed topical corticosteroids and PPIs [1].

This article summarizes the effectiveness of the different alternatives for the dietary treatment of patients with EoE, updates the most relevant information by discussing recent knowledge on empiric elimination diets, and provides practical guidance to achieve the best results with diets in clinical practice.

## 2. Elemental diets: highly effective but commonly infeasible

Elemental diet consists of feeding patients exclusively by a single amino acid-based formula, devoid of antigenic capacity, while all kind of table foods are completely avoided. After the aforementioned first evidence in 1995 [6], subsequent studies, mainly performed in children, further corroborated that elemental diet rapidly induced remission of symptoms and esophageal inflammation in most patients. In a prospective study published by Markowitz et al. in 2003, symptoms improved and eosinophilic infiltration reduced in 49 out of the 51 recruited children after being fed exclusively with elemental formulas (from 33.7 to 1 eos/hpf) [13]. Four additional pediatric retrospective series reproduced these results [11,14–16]. However, a high proportion of children needed to be fed through a nasogastric tube [15].

As for adults, the effectiveness of elemental diets has been assessed in two prospective studies. In the first one, 29 patients were advised to avoid any kind of food except an elemental formula for a 4-week period [17]. Three patients abandoned the study protocol on the very first day and eight more consumed forbidden solid foods during the study period. A pathological infiltration of >15 eos/hpf persisted in only one out of the 18 adults who completed the

study, giving a per-protocol efficacy of 94.4%, which went down to 58.8% when analyzed for intention-to treat. After resuming to a normal diet, inflammation rapidly recurred. The second study involved 21 adults with active disease, but only 17 of them adhered to the diet over a 4-week period; clinico-histological remission of EoE was documented in 12 patients (70.6%) [18].

The overall effectiveness of elemental diet to achieve histologic remission of EoE was estimated in 90.8% in a meta-analysis summarizing studies performed in both children and adults [19], making it the most effective dietary approach for EoE. Lack of response to elemental diets is likely due to poor adherence to such a complicated diet. Another alternative explanation might be the involvement of environmental, rather than food, allergens as triggers for EoE, although cumulative evidence is minimizing its potential role to cause inflammation of EoE [20–22]. However, a variety of reasons make elemental diet unfeasible in clinical practice: to begin with, its poor palatability that requires nasogastric tube in many patients to ensure a proper intake of calories; the negative impact of complete avoidance of any kind of table food on social activities, psychological well-being and HRQoL has been repeatedly noticed [4].

Also, the high cost, not universally reimbursed by insurances, constitutes an additional barrier for implementing elemental diet, and finally, in children under 2 years old or with known feeding dysfunction, long-term avoidance of solid food may lead to delayed oral-motor skill development [23]. The above-mentioned limitations greatly reduce the true possibilities of using exclusive elemental diets for EoE in clinical practice for highly refractory infants and toddlers (among whom the restriction of having no additional food may be better tolerated) as a bridge therapy while waiting for investigational drugs. Patients who wish to remain in remission while investigating the casual role of unusual foods and aeroallergens in their disease are also potential candidates. These utilities, however, have not been adequately assessed yet [1].

## 3. Food allergy testing in EoE: a failed strategy to be avoided

The high efficacy rate of elemental diets demonstrated, with no doubt, that EoE was a food allergy in the vast majority of patients. It was crystal-clear that allergists would develop the following studies, aimed at identifying food triggers by food testing, in order to achieve remission after a diet tailored for each individual.

In the first report published in 2002, Spergel et al. showed that a combination of skin prick testing (SPT) and atopy patch testing (APT) in pediatric EoE provided clinical and histologic remission in 49% of patients after excluding from each child's diet an average of five foods [24]. Among these subjects, the mean peak eosinophil count decreased from 55.8 to 8.4 eos/hpf, accompanied by symptom improvement in all cases. The same researchers updated their results in 2012 and provided a 53% complete remission rate after following an exclusion diet directed by SPT and APT [25]. When allergy testing was

combined with empirical elimination of milk in a hypothetical analysis, regardless of test results, the effectiveness increased up to 77% [24,25].

The main criticism to these studies is that food triggers were not identified by histologic remission, but rather by symptom relapse reported by parents after individual food reintroduction. A low correlation between symptoms and histological activity in EoE has been repeatedly demonstrated [26], which improves when disease-specific validated instruments are used [27]. Regardless of this limitation, a variable sensitivity and specificity of these allergy tests was found, with <10% of positive results in both tests, as well as a low sensitivity to cow's milk, which is the most common food trigger for EoE. The accuracy of SPT and APT to detect milk, wheat and egg, the most common food triggers in EoE as proved by empirical elimination diets, has been also shown to be insufficient to guide clinical practice: Positive predictive values (PPV) for SPT ranged from 26.3% to 86.3% (average 47%), while negative predictive values (NPV) were >90% for multiple foods, but much lower for cow's milk (30%), egg, wheat and soy (79–90%) [24]. Likewise, results for APT followed a similar trend, with PPV ranging from 12% to 86.2% (average 44%), and NPV >90% with the exception of milk (31%). The combination of SPT and APT yielded a poor average PPV (44%) but allowed to increase the average VPN (92%). However, milk continued to show a low NPV (44%) [25]. In parallel, pediatric research groups in Cincinnati also found low NPVs for milk (40%), egg (56%), and wheat (67%) among children with EoE [16]. A position paper of the European Academy of Allergy, Asthma and Immunology stated in 2016 that measuring specific 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, because it does not improve EoE in a significant number of patients [28].

The predictive ability of alternative allergy testing to identify foods responsible for EoE in adult patients was further investigated [29]. Food triggers for EoE were identified in a prospective series of 20/23 adult patients with PPI-refractory EoE who responded to a six-food empiric elimination diet (SFED) and underwent to subsequent food challenge. Five allergy testing modalities were performed at specific intervals, dependent on the response to dietary modification, and failed in identifying food triggers: SPT and serum specific IgE resulted positive to a number of food allergens but did not predict accurately triggers of EoE; APT were always negative with respect to food. All patients had serum IgG levels positive to two or more food antigens, but no correlation with actual triggers was found. Finally, basophil activation tests detected soy in a patient with EoE triggered by milk, egg, wheat, soy, and fish; in the remaining cases it was negative for all food antigens.

Direct esophageal prick testing (EPT) was an imaginative proposal aimed at overcoming the poor predictive capacity of allergy testing in EoE [30], by challenging directly the esophageal mucosa with local injections of allergen extracts. Among the 8 adult EoE patients challenged, 5 showed immediate mucosal blanching and/or total luminal obstruction after mucosal injection of soy ( $n = 2$ ), banana, apple, oats, and

hazelnut. In all patients, luminal obstruction improved allowing the passage of the endoscope around 10 minutes later and was completely gone the following day. No patient showed reaction to milk, wheat or egg, the most common food triggers in EoE. While this study first proves the ability of the esophagus for immediate reactions after local injection, its usefulness to guide dietary therapy remains questionable.

Recently, an increasing role for IgG4 in EoE has been recognized, after a seminal study which demonstrated a 45-fold increase in 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: milk, wheat, egg, and nuts [31]. Additional studies in children and adults confirmed these results [32–35]; tissue IgG4 levels correlated with esophageal peak eosinophil count, degree of histological features, and gene expression level of Th2 cytokines in subjects with EoE [34], thus supporting the potential role of IgG4 in EoE. Prospective trials on the ability of IgG4 testing to guide dietary elimination therapy in EoE were, therefore, warranted. A recently published study developed and assessed a CD4 + T-cell proliferation assay over blood samples obtained from adult patients with well-identified food triggers for EoE [36]. IgG4 assays were subsequently performed on esophageal biopsies obtained from another cohort of adult patients with active EoE, with the five individual foods which provided the best agreement between the proliferation threshold and the known food triggers. After the CD4 + T-cell proliferation and IgG4 assays were complete, a total of 12 individualized diets were created to span the 22 patients who received treatment. After eliminating an average of 3.4 foods for 6 weeks under nutritionist counseling, tissue eosinophil density reduced in three quarters of the patients who were compliant with the diet. However, only 4 out of 19 (21%) had less <15 eos/hpf, a response rate that is even lower than previously reported for targeted elimination approaches using traditional allergy testing.

#### 4. Empiric elimination diet: an evolving approach

In 2006, an empiric diet eliminating six food groups that accounted for the majority of IgE-mediated food reactions (milk, wheat, egg, soy/legumes, nuts, fish/seafood) was reported to induce complete histologic remission in three out of four pediatric patients with EoE. In particular, this SFED protocol utilized no allergy testing, and was thus empiric, based on the concept that avoidance of foods that commonly cause immediate food hypersensitivity could also resolve EoE [11]. Among patients who achieved histologic remission, serial single-food reintroductions followed by repeated endoscopies with biopsies allowed identification of specific food triggers responsible for EoE in each individual patient by documenting recurrence of eosinophilic infiltration [37]. Though it became the standard in clinical practice, the so-called SFED turned out to be quite unpopular for both patients and physicians because of its high level of restriction and the need for numerous endoscopic procedures. However, it was the first reliable method to identify EoE-triggering foods certainly, while allowing us to know the frequency the

different foods trigger and maintain EoE [38]. SFED was essential to develop subsequent simpler empirical dietary therapy regimens.

#### 4.1. Six-food elimination diet

After the first study with a SFED in children [11], research in adults [39,40] demonstrated that this dietary approach induced remission in a similar proportion of patients. A meta-analysis of seven observational studies assessing SFED in patients of all ages provided an extremely homogenous ( $I^2$  statistic = 0) histologic remission rate of around 72% (95% CI, 66–78%) [19], revealing it as the most reproducible dietary approach for EoE. Of note, up to three quarters of patient responders to a SFED have been found to have just one or two causative foods after six food challenges and six endoscopic procedures [37].

Only a minority of patients had nuts, fish, and seafood as food triggers for EoE, thus paving the way for implementation of a simpler and easier elimination diet, the so-called four-food elimination diet (FFED), able to loosen up the level of dietary restriction and to reduce the number of endoscopies and length of time needed to complete the reintroduction process.

#### 4.2. Four-food elimination diet

In an attempt to optimize dietary restrictions and endoscopic procedures for dietary therapy in EoE, the FFED was developed to eliminate the four most common food triggers in EoE elucidated within the SFED studies (cow's milk, wheat, eggs and soy/legumes), while allowing the consumption of the remaining. The first experience with a FFED was published as an abstract by Gonsalves et al. [41], who treated 13 adult patients, 8 out of them achieving histological remission of EoE (<10 eos/hpf) after 6 weeks. Molina-Infante et al. carried out the first research on FFED published as a full-text paper. This prospective multicenter study on 52 adult patients with EoE from Spain showed a 54% histologic remission rate [42]. Six of the 19 (31%) nonresponders to the FFED were successfully rescued with a subsequent SFED.

As for children, the effectiveness of a FFED has subsequently reported by Kagalwalla et al [43]: Seventy-eight patients were prospectively recruited at four medical sites in the USA; after 8 weeks, 50 patients (64%) were in histologic remission, and symptoms score significantly decreased from baseline. The most common food triggers identified were cow's milk (85%), egg (35%), wheat (33%), and soy (19%).

#### 4.3. Step up 2-4-6 food elimination diet

Studies on FFED showed that the food triggers found in more than half of those who responded to this type of diet (especially children) could have been identified by starting with an even simpler approach: a two-food elimination diet (TFED), consisting in withdrawing from the patients' diet cow's milk and wheat, while consuming egg or soy/legume was allowed [42,43]. Accordingly, a step-up approach for dietary therapy in patients with EoE (i.e., eliminating at first the one or two most

common food triggers and subsequently increasing the level of restriction in non-responders) might result in notable advantages. This approach was first assessed in 2018 in the biggest multicenter study conducted so far for diets in EoE, gathering 130 consecutive patients, among whom 25 were children, from 14 centers, mostly in Spain [44]: All patients underwent a TFED (milk and wheat) and non-responders were offered to escalate to a FFED and eventually to a SFED, if histological remission (<15 eos/HPF) was not observed. A TFED led to histologic and symptomatic remission of EoE in 43% of patients. In non-responders, stepping up to a FFED provided remission to 60% of patients. Among non-responder patients, SFED as a rescue therapy increase remission rates overall to 79%. No differences in remission rates for the subsequent diets were found between children and adults.

Compared to a top-down strategy, a step-up approach provides numerous advantages, including reducing endoscopic procedures and shortening the diagnostic process time by 20%, avoiding unnecessary dietary restrictions in most patients, and identifying early responders with few food triggers without need of a SFED. In addition, step-up approach provided evidence that 90% of responders to a TFED or FFED were found to have just one or two causative foods, thus are definitively best candidates for maintenance of EoE by dietary therapy. In contrast, responders to a SFED with previous failure to a TFED and FFED were shown to have three or more food triggers, including nuts and fish/seafood, which discourage undergoing to a SFED due to the limited likelihood of adhering to a proper diet to maintain EoE in remission in the long term, except for really motivated patients.

A retrospective European registry of children from 13 countries has confirmed recently the efficacy reported for the initial step-up elimination diet approach in EoE [45]: SFED induced EoE remission in 68% of patients, a three-food elimination diet (milk, wheat, and egg) in 46%, and a TFED in 32%.

#### 4.4. Milk elimination diet: the next step?

Cow's milk is reported as the most common food trigger for EoE in both children and adults, and cow's milk elimination diet would be a first easier way to check the efficacy of a dietary intervention. Evidence on its effectiveness has been provided in the pediatric literature, where an encouraging histologic remission rate or 61%–65% were provided by earlier studies [14,46]. However, these studies were flawed by methodological issues, as the inclusion of patients with EoE induced after oral milk desensitization to treat IgE-mediated cow's milk allergy [14] and the concomitant initiation of PPIs during cow's milk elimination [46,47], a drug able to achieve clinical and histological remission in 50% of patients with EoE, both overestimating the effect of milk elimination. Data from a better designed retrospective study have been provided recently: 18 out of 31 (58%) children achieved histological remission of EoE after undergoing strict cow's milk elimination [48]. An additional abstract reported on a series of 30 prospectively recruited children with EoE, with 43% of them achieving <15 eos/hpf after 6–8 weeks of milk elimination. One or more symptoms resolved in 58% of responders [49]. A recent retrospective European registry showed much more



disappointing results (25%). In addition, a multicenter randomized trial tried to compare one-food elimination diet (OFED) versus FFED in pediatric patients with EoE from USA [50]. After 12 weeks, patients treated with a FFED ( $n = 25$ ) experienced a significantly greater improve in symptoms (measured with the validated PEESS v2.0 questionnaire [27]), but histological remission was slightly higher among children treated with OFED ( $n = 38$ ). Comparison groups were not balanced so we cannot exclude a randomization bias affecting results of this study, which prevents us from drawing valid conclusions.

At present, no studies on cow's milk elimination diet have been reported in adults. However, a still ongoing randomized trial is comparing the effectiveness of OFED and SFED in adults with EoE (clinicaltrials.gov ID: NCT02778867). Swallowed glucocorticoid therapy is used in participants for whom dietary therapy was not effective. Prospective studies specifically designed to assess the efficacy of milk diet in children and adults are definitely warranted. Table 1 summarizes the results of available studies with milk elimination to treat EoE.

The significant homology between milk from cow, sheep and goat results in clinical cross-reactivity, so elimination diets must include milk from all these mammals [51].

#### 4.5. Step-up empirical food elimination is the most efficient dietary approach

A computer-based simulation model recently compared different clinical strategies for dietary therapy in EoE, by assessing the potential effect of eliminating up to 12 foods known to induce EoE, balanced by the number of endoscopies required to complete the food elimination strategy and identifying culprit foods [52]. In all simulations, always starting with elimination of dairy, the 1,4,8-food and 1,3-food strategies, were the most efficient in identifying foods that induced EoE, resulting in the highest rate of the correct identification with the lesser mean number of endoscopies. In the 1,4,8-food strategy, foods activating EoE were correctly identified in 76.7% of patients after performing a mean of 4.1 endoscopies, while the 1,3-food strategy identified culprit foods in 42.76% of patients after a mean of 3.4 endoscopies. Further studies on real patients should confirm the predictions of this model. Figure 1 summarizes histologic remission rates achieved with the different modalities of empiric elimination diets in EoE.

#### 5. Long term efficacy and safety of dietary therapy for EoE

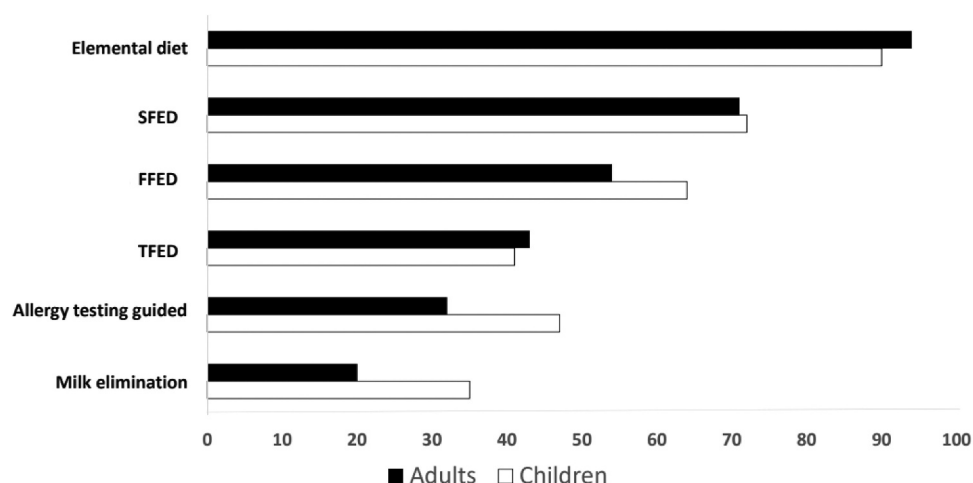
Once food triggers responsible for EoE have been identified in each particular patient, long-term avoidance is advisable to maintain drug-free disease remission. Along the last decade, up to five observational studies have provided evidence on the ability of dietary therapy in maintaining patients asymptomatic and with no active inflammation in esophageal biopsies for a period of 1 to 4 years.

In 2011 Kagalwalla et al. reported that avoiding food groups triggering EoE identified through sequential food challenge maintained disease in remission for a period of up to 4 years [37]: Five patients restricted from their diets culprit foods in the long run while endoscopies were repeated every

Table 1. Available published studies assessing the efficacy of empirical cow's milk elimination diet to treat EoE.

Study, year of publication	Reference	Country	Patients' age (years old)	Study design	n (male)	Study outcomes	Comments
Kagalwalla AF, 2012	[11]	USA	Mean: 5.5	Retrospective, single center case series	17 (71%)	65% had <15 eos/hpf 41% had $\leq 1$ eos/hpf	Inclusion of patients with "overcome" IgE-mediated allergy to milk
Kruszewski PG, 2016	[46]	USA	2–18	Prospective, multicenter, comparative case series	16 (65%)	64% had <15 eos/hpf	All patients received PPI therapy concomitantly with diet
Wechsler JB, 2017	[49]	USA	Mean: 8	Prospective, multicenter case series	30 (73%)	43% had <15 eos/hpf Symptoms resolved in 58%	Exclusively published as an abstract
Teoh T, 2019	[48]	Canada	<16	Retrospective, single center study	31 (84%)	58% had <15 eos/hpf 23% had <1 eos/hpf 77% had decreased eosinophils Symptoms improved in 90%	Liberalized cow's milk elimination improved EoE in only 23% of patients.
Hoofien A, 2019	[45]	13 European Countries	n.a.	Retrospective, multicenter, online database	16 (n.a.)	25% had <15 eos/hpf	Study with a high risk of bias
Kliewer, 2019	[50]	USA	6–17	Randomized controlled trial	38 (n.a.)	44.1% had <15 eos/hpf	Non reliable results due to a high risk of bias
Wong J, 2020	[47]	USA	0.6–20.8	Prospective, multicenter, comparative case series	102 (76%)	56.9% had <15 eos/hpf	90 (88.2%) patients received PPIs concomitantly with diet

eos/hpf: eosinophils per high-power field; n.a.: not available; PPI: proton pump inhibitor



**Figure 1.** Histologic remission rates broken down by age group and shown by different modalities of dietary therapy (elemental diet, empiric elimination diets, and allergy testing-guided elimination diet) for EoE. SFED: six-food elimination diet; FFED: four food elimination diet; TFED: two-food elimination diet.

1–2 years. During follow-up no treatment-related complications were noted and none demonstrated nutrient deficiencies or growth deceleration. However, all cases relapsed on rechallenge with known food triggers.

As for adults, two studies reported that all patients who strictly avoided foods known to trigger EoE had their disease in clinical and histological remission for up to 3 years [39,40]. Two more recent studies in adults confirmed that adherence to diet maintained durable histologic remission for up to 2 years of follow-up, together with sustained improvement of symptoms and reversion of endoscopic features of EoE [53,54]. However, a high rate of non-adherence and diet cessation were reported in these last studies, which led to disease recurrence. In fact, adherence represents a real problem, especially for adults, that limits the number of patients remaining on a food elimination diet in the long term. Identification of barriers to adherence to further define the optimal candidates for dietary treatment is essential to succeed with dietary treatment in the long term.

As dietary therapy is posed as a long-term intervention, some concerns have arisen in the literature regarding the effect of elimination diets on anthropometric profiles and growth specially in children with EoE [43,55], especially after recent longitudinal studies of children with persistent IgE-mediated cow's milk allergy showing an increased risk of not reaching their growth potential in adulthood [56,57]. Despite dietary therapy is considered to be generally safe in the long term, nutritional monitoring and appropriate dietary intervention are of particular importance in at-risk individuals, including children with IgE-mediated food allergies who avoid more than 3 food groups [58]. Although weight and body mass index can reduce slightly in children after starting an empiric elimination diet, they increase from baseline after completing food reintroduction [43]. In any case, we advise regular assessment of macro and micronutrients in patients of all ages treated with elimination diets by a dietitian with counseling regarding replacement [58,59]. A sustained and prolonged food avoidance leading to loss of immunological tolerance to food involved in triggering EoE so that a serious reaction

to it can be generated in case of accidental consumption is an additional potential risk that should be also considered [59]. The potential effect of milk, wheat, and legume avoidance on intestinal microbiota (sources of prebiotic carbohydrates) deserves further consideration.

## 6. Barriers and limitations for setting up dietary therapy for EoE

Dietary therapy for EoE is not a panacea, and despite full adherence, a proportion of patients will never respond. In addition, diet abandonment and lack of adherence are not uncommon, especially in adolescents and adults, thus frustrating the efforts, resources and time invested in this treatment choice. The decision to set up a dietary treatment must be shared and agreed by the patients and/or their parents, who are the ones who will take most of the effort. Dietary therapy is thus patient-centered and before initiating it, potential short and long-term barriers should be identified [60].

To begin with, patients suffering from IgE-mediated food allergies (a common comorbid condition in children with EoE) or those who are subjected to additional food restrictions, as gluten-free diet for patients with celiac disease, are not the best candidates for dietary therapy [61]. EoE usually will not be caused by food patients usually avoid so additional food restrictions to treat EoE should be added to the former; extensive food restrictions will impair HRQoL by enormously hindering cooking or social life.

Patient lifestyle and their family habits should also be considered; the initial phases of an elimination diet are the most restrictive and make it virtually impossible to eat at restaurants or consuming highly processed products. In addition to the time needed to buy food stuffs and cooking them at home, patients' work and school schedules must be taken into account. If a patient cannot usually have lunch at home or take his/her prepared food to work or school, a proper adherence to the diet will not be guaranteed. Parents, caregivers or family members responsible for providing food to patients must be informed and have the skills to support the patient's

diet [58]. Social events that revolve around food, such as weddings or corporate meals, should be restricted during the study period with an empiric elimination diet.

Elimination diets entail additional expenses for patients with EoE or their families. Difficulties in finding processed foods free of milk, gluten, eggs, or soy make it necessary to buy unprocessed foods in grocery shops instead of supermarkets if food allergen labeling is not complete, and cook them at home. A SFED resulted in a 17.4% weekly cost increase regarding a regular diet in the United States [62]. Patients must be informed of this cost and logistical burden when selecting dietary therapy to treat EoE.

Nutritionist resources have been proposed as essential when implementing dietary therapy for EoE [58,59], including to screen for nutritional risks and nutrient deficiencies. Certainly, EoE may have detrimental effects in small children and toddlers due to poor intake and specific food-related symptoms. However, most of patients with EoE develop coping strategies that allow them to maintain a proper nutritional status, therefore macro or micronutrients deficiencies are rarely found in older children, adolescents and adults [63,64]. It is preferable to provide individualized dietary advice regarding the number of foods that are eliminated and the nutritional quality of those that are allowed. The literature provided evidence, however, that involving a nutritionist is not necessarily required to succeed with dietary therapy, if written practical advice is provided to patients or parents including detailed instructions to read food labeling, lists of ingredient and recommended samples menus [40,42–44].

Finally, as repeated endoscopies with biopsies are an essential component in a food reintroduction protocol [65], this should be discussed with patients to ensure willingness to proceed. Patients accept repeated endoscopies and therefore dietary therapy if systematic sedation is provided for all endoscopic procedures. Flexibility in scheduling and rescheduling endoscopic appointments depending on the histological results is also advisable [66].

## 7. Keys to succeed in dietary therapy for EoE

The success of the diet is based on adequate patient selection, with a patient-based strategy designed to overcome potential barriers. Some practical advices are proposed below:

### 7.1. Selecting the appropriate patient

Best candidates for dietary elimination are motivated patients who are willing to undergo repeated endoscopic procedures and empowered to effectively manage the limitations that an extensive diet may impose on their social or work activities. When to start a diet should also be considered, advising against vacations or periods with planned trips in the forthcoming few weeks. Patients with evidence of nutritional deficiencies or those with other concomitant food allergies or intolerances already on dietary restriction should be considered to be better managed with PPIs or swallowed topic steroids.

### 7.2. Discuss alternative therapeutic options before taking a decision

Dietary elimination represents a first line therapy that should be offered as an alternative to PPIs and topical steroids, or after failure of the aforementioned treatments [12]. Detailed information on expected remission rates obtained with each option should be provided to patients and/or their parents, with pros and cons of each treatment plan and trying to identify the goals of the dietary revised. Severe symptomatic patients may benefit best from swallowed topical corticosteroids, and dietary therapy can be further tested while not receiving topical steroid therapy [67].

### 7.3. Select the appropriate dietary strategy

A step-up empiric elimination diet should be currently offered to patients of all ages, as it is a reasonable initial dietary approach for EoE. However, a FFED provides a higher remission rate and might be acceptable for adults, while young children could benefit of assessing initially empiric milk elimination. Elimination of more than four food groups should be discouraged; 90% of patients who did not responded to a FFED had 3 or more foods independently triggering EoE [44], which might make long-term restriction unfeasible in real life, leading to the abandonment of dietary therapy.

A step-up approach for empiric elimination diet has been demonstrated to be cost-effective in terms of reducing the number of endoscopies and the time required to complete a food reintroduction protocol to identify food triggers for EoE [44,52]. All elimination diets should be instituted for a minimum of 6 weeks and always followed by esophageal biopsies applied during an endoscopic procedure. The patient must be aware that neither symptoms nor endoscopic features alone without histologic results can accurately guide the reintroduction process [65]. Elemental diets and allergy testing-directed food elimination are no longer recommended out of investigational protocols or in special situations.

### 7.4. Response to diet and subsequent food reintroduction

Patients should begin with the end in mind. Once disease remission has been achieved with diet, the reintroduction process can take many months. If histological remission is documented after eliminating several foods or groups of foods, these should be reintroduced individually while continuing the diet (one at a time), generally for a minimum of 6 weeks. However, a recent study suggested that 2 weeks may be sufficient to induce the histopathological changes that define active EoE after food challenge [68]. The more food removed, the longer the food reintroduction process will take. Intermittent breaks during the process are feasible and strongly recommended. The final goal of dietary elimination and reintroduction will always be identifying which foods trigger esophageal inflammation to design an individualized diet that avoids culprit food antigens in the long term [66].



### 7.5. Ensure dietary antigens are eliminated from the diet

The need to restrict multiple food allergens makes it difficult both buying adequate food and cooking. Patients should be provided with clear written information about how to read and interpret labeled food products, and what specific foods frequently consumed are permitted and prohibited. To improve the control on each component of a recipe, we strongly recommend patients, whenever possible, cooking by themselves at home, instead of consuming industrially prepared meals. In addition, patients should be instructed on how to avoid cross-contamination between their own diet and that of the other family members. Cow's milk proteins show cross reactivity with those of sheep's and goat's milk, so all mammalian milk derivatives should also be avoided. Milk protein hydrolyzates, however, are well tolerated by EoE patients [69]. As for wheat, risk of cross-contamination and concerns of possible cross-reactivity among related grains of barley and rye [70], led most of recent studies to restrict gluten-containing grains in empiric elimination diets [42,44]. In contrast, expert opinion advised against extending wheat elimination to other gluten-containing grains [71]. Studies on clinical cross-reactivity among gluten-containing grains are still required in EoE.

### 7.6. Coping with avoidance of common foods

Milk, wheat, egg, and, to a lesser extent, soy/legumes, the major triggers in EoE, are foods commonly consumed and widely distributed in Western diets. Avoiding either might be troublesome for patients, and practical advice to effectively replace some foods for appropriate alternatives in terms of its nutritional and culinary capacities, while limiting the impact of the diet on their social activities, is required. The participation of a dietitian can help the patient with resources for cooking varied and nutritious menus.

Diet compliance problems often arise in older children, adolescents, and young adults, so more emphasis should be placed on the above aspects in these patients.

## 8. Uncertainties and unsolved issues of dietary therapy in EoE

Accumulated evidence shows that EoE is essentially triggered by food antigens, with an increasingly less recognized role for environmental allergens. However, the different dietary approaches have provided maximum efficacy rates of up to 70%–96% [19]. The main differences between elemental and empiric SFED diets basically consist of the possibility of consuming meat, fruits and vegetables, which potentially explains the 20% difference in the effectiveness of both interventions. Meats are minimally allergenic [72], and are usually cooked thus more of their allergenic proteins denatured by the effect of heat. Fruits and vegetables, therefore, would be considered as major triggers for EoE in nonresponders who properly performed a SFED or more extended empiric schemes. In fact, most adult EoE patients exhibit sensitization to cross-reactive panallergen components, including profilins [73] and lipid transfer proteins (LPT) [74], which are mostly found in

food of vegetal origin. Similar results have been also provided in children [75].

From the initial description of the SFED in 2006, a 6-week course of treatment has been considered the minimum length of time to achieve histologic remission of EoE. Most trials have followed this rule [40,41,44,68], with only a minority prolonging food restriction before endoscopy up to 12 weeks [50,76]. It is likely that the longer the duration of the restriction, the more difficult it will be to maintain adherence to the diet [47], but the effectiveness of the diet could be increased [76]. After achieving remission by eliminating several foods or food groups, they should be individually reintroduced one at a time, while continuing on the diet. Patients should be advised to consume or be exposed to a certain amount of each reintroduced food almost daily, with an endoscopic procedure after each individual food reintroduction. The accurate duration of each food challenge remains unknown; most authors have considered that food reintroduction should be undertaken for a minimum of 6 weeks, but some trials obtained equivalent results after only 2-week challenges [29,68], conditioned to the lack of recurrence of inflammation in the immediately preceding endoscopy.

Sedation for endoscopic procedures is key to engage patients with empiric elimination diets. Propofol is not contraindicated in patients with EoE sensitized or allergic to egg, soy or peanut irrespective of age [77–79]. Repeated propofol sedation is considered safe, even in children [80].

Dietary therapy constitutes both an induction and maintenance treatment of EoE, and adherent patients maintain remission in the long term. A number of patients might develop spontaneous tolerance to culprit food after prolonged remission, while some others could lose response because of airborne allergens [22]. Further studies should be carried out to shed light on this issue. Finally, some patients with milk-induced EoE have been documented to tolerate cooked milk [48,81]. Nevertheless, the proportion of patients and its impact on improving HRQoL or inducing subsequent milk tolerance merit further evaluation.

## 9. Expert opinion

Treatment of EoE is by far the aspect that has changed the most in the last decade [1], and dietary therapy has not been an exception. Currently, diet represents a first-line therapy for induction and maintenance of remission of EoE. Despite its moderate effectiveness, dietary therapy represented the preferred choice to treat patients after PPI or swallowed topical steroids failure, according to a recent multicenter registry of clinical practice [12]. In fact, diet is the only therapy that targets the primary cause of EoE; its low cost and excellent safety profile definitely constitute additional advantages. However, the high level of restriction imposed by elemental diets or SFED (the only alternatives with an efficacy comparable to the most effective drugs in the treatment of EoE) limited the role of dietary therapy as an acceptable alternative for many patients and doctors dealing with this disease. Only over the last few years, adoption of new simpler dietary schemes, which begin with a minimum level of restriction, progress to a greater one in case of non-response, and applies

the maximum restriction to exceptional cases or highly motivated patients, has represented a change from a 'top down' approach (starting with the highest level of restriction) to a much more rational 'step up' strategy.

Due to multiple disadvantages and obstacles inherent to elemental diets for EoE, and the neglected utility of current allergy testing to address dietary restrictions in these patients, dietary approaches based on empiric food elimination have become widespread in recent years, as the only alternative capable of precisely identifying and restricting the foods responsible for EoE in each individual patient. Despite its high level of restriction, experience on SFED allowed to know that the most common food triggers in children and adults from the United States, Europe, and Australia are by far cow's milk, followed by wheat/gluten and egg. Legumes seem to be important solely in Spain and other Mediterranean countries, where they are regularly consumed, while soy predominates in the United States. The change in the paradigm on use of dietary therapy for EoE that occurred in the last few years determines that an empiric elimination diet step-up strategy is now well-established as the initial approach for dietary treatment. The advantages of starting with a TFED are clearly demonstrated in clinical practice [44] and milk elimination also begins to be shown as an efficient strategy [47,48]; computer-based simulation models support these approaches [52] and favor considering dietary therapy as a real, effective, and feasible option to be offered to patients with EoE, which corrects the food allergy that triggers the disease and dispenses young patients with the chronic use of medications.

However, almost all studies dealing with dietary therapy of EoE have been carried out in countries of European cultural (and culinary) origin, but the foods that cause EoE here may not be the same for other regions [82]. Differences in geographical patterns of food consumption among countries have not been studied yet.

Success of dietary therapy for EoE mostly relies on providing patients with simple instructions to identify food allergens and practical tips on how to replace foods to avoid with permitted alternatives. Clinicians also need clear instructions to effectively put into practice dietary recommendations [66]. Variations among different available diets (eliminating wheat against gluten, cow's milk or also those of other mammals to avoid cross-reactivity) may not contribute to homogenize standards in clinical practice. Recommendations should not be based on expert judgment [71], but rather on well-documented empirical evidence.

Aside of cross-reactivity matters, the optimal duration of dietary elimination required to induce remission needs to be clarified, as this is a critical issue of high relevance. Up to now, the duration of dietary therapy required to define success have arbitrarily been defined in around 6 weeks, and the impact of different lengths of initial treatment has been seldom assessed [76]. Some evidence has suggested that dense eosinophilic infiltration in baseline mucosal biopsies could require a longer diet duration to achieve complete histological remission [40,76]. However, a 12-week duration led to a lower than expected efficacy in other studies [50]. Similarly, the duration of food challenge should be properly defined in

order to assess the impact of short challenge periods in reducing the study time required by patients to complete food reintroduction.

Finally, other unsolved issues for dietary therapy in EoE include its effects in reversing subepithelial fibrosis and its potential impact on HRQoL of patients with EoE. On the first matter, one single study demonstrated improvements in esophageal body distensibility by measured with endoFLIP achieved with diet (and medical) therapies in the short term without need of esophageal dilation [83]. Detractors of dietary therapy for EoE have claimed that eliminating staples foods from a regular diet may impair patients' HRQoL. However, no study has appropriately evaluated the effects of long-term food avoidance on HRQoL of EoE patients. Any effective therapy able to induce symptomatic control and histologic remission of EoE potentially increases HRQoL [4]. However, several factors may contribute to the negative impact of EoE on HRQL, despite the fact patients could have achieved remission of the disease. These included its chronic nature, a management that entails a demanding and permanent drug-based of restrictive diet, the possibility of finding other affected family members, the limitations that a diet imposes on family and social activities, and the psychological distress that all these factors generate. Experience in celiac disease has shown that commencing and following a gluten-free improves both symptoms and HRQoL, despite the restrictions this type of diet imposes [84–86]. The degree of adherence to a gluten-free diet has been shown to be an essential factor in the HRQL of celiac patients, with better results in patients with total adherence [84,87]. These results may mirror what happens in EoE, where the HRQoL measured with a disease-specific validated instrument showed no difference between adult patients who maintained controlled their disease with diet or drugs [88].

## Funding

This paper was not funded.

## Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

## Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

## ORCID

Alfredo J Lucendo  <http://orcid.org/0000-0003-1183-1072>

Javier Molina-Infante  <http://orcid.org/0000-0003-1204-0571>

## References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Lucendo AJ, Molina-Infante J, Arias Á, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. *United Eur Gastroenterol J*. 5(3): 335–358. 2017.
- **Updated evidence-based recommendations for the multidisciplinary management of patients with EoE. Dietary modifications, PPIs and swallowed topic corticosteroids are proposed as first line therapies; esophageal dilation should be considered in patients with dysphagia/food impaction unresponsive to anti-inflammatory treatment.**
2. Navarro P, Arias Á, Arias-González L, et al. Systematic review with meta-analysis: the growing incidence and prevalence of eosinophilic oesophagitis in children and adults in population-based studies. *Aliment Pharmacol Ther*. 2019;49(9):1116–1125.
3. Dellon ES, Hirano I. Epidemiology and natural history of eosinophilic esophagitis. *Gastroenterology*. 2018;154(2):319–332.
4. Lucendo AJ, Arias-González L, Molina-Infante J, et al. Systematic review: health-related quality of life in children and adults with eosinophilic oesophagitis-instruments for measurement and determinant factors. *Aliment Pharmacol Ther*. 2017;46(4):401–409.
5. Greuter T, Bussmann C, Safroneeva E, et al. Long-term treatment of eosinophilic esophagitis with swallowed topical corticosteroids: development and evaluation of a therapeutic concept. *Am J Gastroenterol*. 2017;112(10):1527–1535.
6. Kelly KJ, Lazenby AJ, Rowe PC, et al. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology*. 1995;109(5):1503–1512.
- **First report confirming the etiologic role of food antigens in EoE. Eight children with EoE refractory to acid secretion blockers and Nissen fundoplication achieved complete remission after elemental diet for a minimum of 6 weeks.**
7. Arias Á, Lucendo AJ. Molecular basis and cellular mechanisms of eosinophilic esophagitis for the clinical practice. *Expert Rev Gastroenterol Hepatol*. 2019;13(2):99–117.
8. Faubion WA, Perrault J, Burgart LJ, et al. Treatment of eosinophilic esophagitis with inhaled corticosteroids. *J Pediatr Gastroenterol Nutr*. 1998;27(1):90–93.
9. Chuang M-YA, Chinnaratha MA, Hancock DG, et al. Topical steroid therapy for the treatment of Eosinophilic esophagitis (EoE): a systematic review and meta-analysis. *Clin Transl Gastroenterol*. 2015;6:e82.
10. Lucendo AJ, Arias Á, Molina-Infante J. Efficacy of proton pump inhibitor drugs for inducing clinical and histologic remission in patients with symptomatic esophageal eosinophilia: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2016;14(1):13–22.
11. Kagalwalla AF, Sentongo TA, Ritz S, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 4(9): 1097–1102. 2006.
- **Seminal first study proving a 74% effectiveness for a 6-week empiric six-food elimination diet (SFED). The SFED consisted of eliminating empirically the six-food groups typically associated with food allergy in children from Chicago (cow's milk, wheat, egg, soy, nuts, fish, and seafood).**
12. Laserna-Mendieta EJ, Casabona S, Savarino E, et al. Efficacy of therapy for eosinophilic esophagitis in real-world practice. *Clin Gastroenterol Hepatol*. 2020. DOI:10.1016/j.cgh.2020.01.024.
13. Markowitz JE, Spergel JM, Ruchelli E, et al. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. *Am J Gastroenterol*. 2003;98(4):777–782.
14. Kagalwalla AF, Amsden K, Shah A, et al. Cow's milk elimination. *J Pediatr Gastroenterol Nutr*. diciembre de. 2012;55(6):711–716
15. Liacouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc*. diciembre de. 2005;3(12):1198–1206.
16. Henderson CJ, Abonia JP, King EC, et al. Comparative dietary therapy effectiveness in remission of pediatric eosinophilic esophagitis. *Journal of Allergy and Clinical Immunology*. 2012;129(6):1570–1578
17. Peterson KA, Byrne KR, Vinson LA, et al. Elemental diet induces histologic response in adult eosinophilic esophagitis. *Am J Gastroenterol*. mayo de. 2013;108(5):759–766.
18. Warners MJ, Vlieg-Boerstra BJ, Verheij J, et al. Elemental diet decreases inflammation and improves symptoms in adult eosinophilic oesophagitis patients. *Aliment Pharmacol Ther*. 2017;45(6):777–787.
19. Arias A, Gonzalez-Cervera J, Tenias JM, et al. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. *Gastroenterology*. junio de. 2014;146(7):1639–1648.
- **First meta-analysis on dietary therapy for EoE in children and adults, showing consistent and high effectiveness for elemental diet and six-food empiric elimination diet. Large heterogeneity and inconsistent poor results were found for allergy testing-guided diet, especially in adult patients.**
20. Lucendo AJ, Arias A, Redondo-Gonzalez O, et al. Seasonal distribution of initial diagnosis and clinical recrudescence of eosinophilic esophagitis: a systematic review and meta-analysis. *Allergy*. 2015;70(12):1640–1650.
21. Egan M, Atkins D. what is the relationship between eosinophilic esophagitis (eoe) and aeroallergens? Implications for allergen immunotherapy. *Curr Allergy Asthma Rep*. 2018;18(8):43.
22. Guajardo JR, Zegar-Bustamante MA, Brooks EG. Does aeroallergen sensitization cause or contribute to eosinophilic esophagitis? *Clin Rev Allergy Immunol*. 2018;55(1):65–69.
23. Delaney AL, Arvedson JC. Development of swallowing and feeding: prenatal through first year of life. *Dev Disabil Res Rev*. 2008;14(2):105–117.
24. Spergel JM, Beausoleil JL, Mascarenhas M, et al. The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. *J Allergy Clin Immunol*. febrero de. 2002;109(2):363–368.
25. Spergel JM, Brown-Whitehorn TF, Cianferoni A, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy Clin Immunol*. 2012;130(2):461–467.
26. Pentiu S, Putnam PE, Collins MH, et al. Dissociation between symptoms and histological severity in pediatric eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr*. 2009;48(2):152–160.
27. Martin LJ, Franciosi JP, Collins MH, et al. Pediatric Eosinophilic Esophagitis Symptom Scores (PEESS v2.0) identify histologic and molecular correlates of the key clinical features of disease. *J Allergy Clin Immunol*. 2015;135(6):1519–1528.
28. Simon D, Cianferoni A, Spergel JM, et al. Eosinophilic esophagitis is characterized by a non-IgE-mediated food hypersensitivity. *Allergy*. 2016;71(5):611–620.
- **Consensus report mostly made by a panel of international allergists, immunologist and gastroenterologists calling our attention to EoE as an allergic disease largely independent of IgE, recommending against performance of IgE food testing.**
29. Philpott H, Nandurkar S, Royce SG, et al. Allergy tests do not predict food triggers in adult patients with eosinophilic oesophagitis. A comprehensive prospective study using five modalities. *Aliment Pharmacol Ther*. 2016;44(3):223–233.
- **Comprehensive study demonstrating the inaccuracy of all available blood and skin food allergy tests to identify triggering foods in adult EoE patients.**
30. Warners MJ, Terreehorst I, van den Wijngaard RM, et al. Abnormal responses to local esophageal food allergen injections in adult patients with eosinophilic esophagitis. *Gastroenterology*. 2018;154(1):57–60.
31. Clayton F, Fang JC, Gleich GJ, et al. Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. *Gastroenterology*. 2014;147(3):602–609.32.
32. Mohammad N, Avinashi V, Chan E, et al. Pediatric eosinophilic esophagitis is associated with increased lamina propria

- immunoglobulin G4-positive plasma cells. *J Pediatr Gastroenterol Nutr.* 2018;67(2):204–209.
33. Schuyler AJ, Wilson JM, Tripathi A, et al. Specific IgG4 antibodies to cow's milk proteins in pediatric patients with eosinophilic esophagitis. *J Allergy Clin Immunol.* 2018;142(1):139–148.
  34. Rosenberg CE, Mingler MK, Caldwell JM, et al. Esophageal IgG4 levels correlate with histopathologic and transcriptomic features in eosinophilic esophagitis. *Allergy.* 2018;73(9):1892–1901.
  35. Wright BL, Kulis M, Guo R, et al. Food-specific IgG4 is associated with eosinophilic esophagitis. *J Allergy Clin Immunol.* 2016;138(4):1190–1192.
  36. Dellon ES, Guo R, McGee SJ, et al. A novel allergen-specific immune signature-directed approach to dietary elimination in eosinophilic esophagitis. *Clin Transl Gastroenterol.* 2019;10(12):e00099.
  37. Kagalwalla AF, Shah A, Li BUK, et al. Identification of specific foods responsible for inflammation in children with eosinophilic esophagitis successfully treated with empiric elimination diet. *J Pediatr Gastroenterol Nutr.* 2011;53(2):145–149.
  - **First description of the method to identify food allergens responsible for EoE by sequential food reintroduction in pediatric patients who achieved remission of EoE after an empirical six-food elimination diet.**
  38. Lucendo AJ. Meta-analysis-based guidance for dietary management in eosinophilic esophagitis. *Curr Gastroenterol Rep.* 2015;17(10):464.
  39. Gonsalves N, Yang G-Y, Doerfler B, et al. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. *Gastroenterology.* 2012;142(7):1451–1459.
  - **First study published on empiric six-food elimination diet to treat EoE in adult patients, that shows quite similar results to those shown among pediatric patients.**
  40. Lucendo AJ, Arias A, Gonzalez-Cervera J, et al. Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. *J Allergy Clin Immunol.* 2013;131(3):797–804.
  - **The most extensive study using six-food elimination diet in adults with EoE in Europe, which provides equivalent results to American studies. Data on sustained remission for up to 3 years are provided.**
  41. Gonsalves N, Doerfler B, Schwartz S, et al. Prospective trial of four food elimination diet demonstrates comparable effectiveness in the treatment of adult and pediatric eosinophilic esophagitis. *Gastroenterology.* 2013;144(Suppl 1):S-154.
  42. Molina-Infante J, Arias A, Barrio J, et al. Four-food group elimination diet for adult eosinophilic esophagitis: A prospective multicenter study. *J Allergy Clin.* 2014;134(5):1093–1099.
  - **The first evaluation of an empiric four-food elimination diet in adults with EoE; nonresponders were rescued with a six-food elimination diet.**
  43. Kagalwalla AF, Wechsler JB, Amsden K, et al. Efficacy of a 4-food elimination diet for children with eosinophilic esophagitis. *Clin Gastroenterol Hepatol.* 2017;15(11):1698–1707.
  - **A multicenter study evaluating an empiric four-food elimination diet in children provided a 64% remission rate.**
  44. Molina-Infante J, Arias A, Alcedo J, et al. Step-up empiric elimination diet for pediatric and adult eosinophilic esophagitis: the 2–4–6 study. *J Allergy Clin Immunol.* 2018;141(4):1365–1372.
  - **First study evaluating a step-up approach with empiric elimination diets in both children and adults. Due to several advantages, like time and endoscopies saved alongside with early identification of patients with few food triggers, this strategy should be now at the forefront of dietary interventions.**
  45. Hoofien A, Dias JA, Malamisura M, et al. Pediatric eosinophilic esophagitis: results of the european retrospective pediatric eosinophilic esophagitis registry (RetroPEER). *J Pediatr Gastroenterol Nutr.* 2019;68(4):552–558.
  46. Kruszewski PG, Russo JM, Franciosi JP, et al. Prospective, comparative effectiveness trial of cow's milk elimination and swallowed fluticasone for pediatric eosinophilic esophagitis. *Dis Esophagus.* 2016;29(4):377–384.
  47. Wong J, Goodine S, Samela K, et al. Efficacy of dairy free diet and 6-food elimination diet as initial therapy for pediatric eosinophilic esophagitis: a retrospective single-center study. *Pediatr Gastroenterol Hepatol Nutr.* 2020;23(1):79–88.
  48. Teoh T, Mill C, Chan E, et al. Liberalized versus strict cow's milk elimination for the treatment of children with eosinophilic esophagitis. *J Can Assoc Gastroenterol.* 2019;2(2):81–85.
  - **The first full-text study in assessing a milk-elimination diet in children with EoE that has been developed with a proper methodological design.**
  49. Wechsler JB, Schwartz S, Ross J, et al. Cow's milk elimination for treatment of eosinophilic esophagitis: a prospective pediatric study. *Gastroenterology.* 2017;152(5):S855.
  50. Kliewer K, Aceves SS, Atkins D. Efficacy of 1-Food and 4-food elimination diets for pediatric eosinophilic esophagitis in a randomized multi-site study. *Gastroenterology.* 2019;156(6Suppl 1):S-172-S-173.
  51. Järvinen KM, Chatchatee P. Mammalian milk allergy: clinical suspicion, cross-reactivities and diagnosis. *Curr Opin Allergy Clin Immunol.* 2009;9(3):251–258.
  52. Zhan T, Ali A, Choi JG, et al. Model to determine the optimal dietary elimination strategy for treatment of eosinophilic esophagitis. *Clin Gastroenterol Hepatol.* 2018;16(11):1730–1737.
  53. Reed CC, Fan C, Koutlas NT, et al. Food elimination diets are effective for long-term treatment of adults with eosinophilic esophagitis. *Aliment Pharmacol Ther.* 2017;46(9):836–844.
  54. Philpott H, Nandurkar S, Royce SG, et al. A prospective open clinical trial of a proton pump inhibitor, elimination diet and/or budesonide for eosinophilic esophagitis. *Aliment Pharmacol Ther.* 2016;43(9):985–993.
  55. Cotton CC, Durban R, Dellon ES. Illuminating elimination diets: controversies regarding dietary treatment of eosinophilic esophagitis. *Dig Dis Sci.* 2019;64(6):1401–1408.
  56. Robbins KA, Wood RA, Keet CA. Persistent cow's milk allergy is associated with decreased childhood growth: a longitudinal study. *J Allergy Clin Immunol.* 2020;145(2):713–716.
  57. Sinai T, Goldberg MR, Nachshon L, et al. Reduced final height and inadequate nutritional intake in cow's milk-allergic young adults. *J Allergy Clin Immunol Pract.* 2019;7(2):509–515.
  58. Groetch M, Venter C, Skypala I, et al. Dietary therapy and nutrition management of eosinophilic esophagitis: a work group report of the American Academy of Allergy, Asthma, and Immunology. *J Allergy Clin Immunol Pract.* 2017;5(2):312–324.
  59. Bashaw H, Schwartz S, Kagalwalla AF, et al. Tutorial: nutrition therapy in eosinophilic esophagitis-outcomes and deficiencies. *JPEN J Parenter Enteral Nutr.* 2020;44(4):600–609.
  60. Kliewer KL, Cassin AM, Venter C. Dietary therapy for eosinophilic esophagitis: elimination and reintroduction. *Clin Rev Allergy Immunol.* 2018;55(1):70–87.
  61. Lucendo AJ, Arias A, Tenias JM. Systematic review: the association between eosinophilic esophagitis and coeliac disease. *Aliment Pharmacol Ther.* 2014;40(5):422–434.
  62. Asher Wolf W, Huang KZ, Durban R, et al. The six-food elimination diet for eosinophilic esophagitis increases grocery shopping cost and complexity. *Dysphagia.* 2016;31(6):765–770.
  63. Mehta P, Furuta GT, Brennan T, et al. Nutritional state and feeding behaviors of children with eosinophilic esophagitis and gastroesophageal reflux disease. *J Pediatr Gastroenterol Nutr.* 2018;66(4):603–608.
  64. Colson D, Kalach N, Soulaïnes P, et al. The impact of dietary therapy on clinical and biologic parameters of pediatric patients with eosinophilic esophagitis. *J Allergy Clin Immunol Pract.* 2014;2(5):587–593.
  - **The first demonstration that the nutritional status of children with EoE was not worsened in the short term by an extensive empiric six-food elimination diet.**
  65. Godwin B, Wilkins B, Muir AB. EoE disease monitoring: where we are and where we are going. *Ann Allergy Asthma Immunol.* 2020;124(3):240–247.
  66. Molina-Infante J, Lucendo AJ. Dietary therapy for eosinophilic esophagitis. *J Allergy Clin Immunol.* 2018;142(1):41–47.



67. Lucendo AJ, Molina-Infante J. Treatment of eosinophilic esophagitis with diets: an update. *Minerva Gastroenterol Dietol*. 2020;66(2):124-135.
68. Eckmann JD, Ravi K, Katzka DA, et al. Efficacy of atopy patch testing in directed dietary therapy of eosinophilic esophagitis: a pilot study. *Dig Dis Sci*. 2018;63(3):694-702.
- **A well designed demonstration that atopic patch testing (APT) does not reliably predict food triggers identified by six-food elimination diet in adult patients with EoE. As a result, APT does not have a role in the evaluation of these patients.**
69. Lucendo AJ, Arias A, Gonzalez-Cervera J, et al. Tolerance of a cow's milk-based hydrolyzed formula in patients with eosinophilic esophagitis triggered by milk. *Allergy*. 2013;68(8):1065-1072.
70. Doerfler B, Bryce P, Hirano I, et al. Practical approach to implementing dietary therapy in adults with eosinophilic esophagitis: the Chicago experience. *Dis Esophagus*. 2015;28(1):42-58.
71. Kliewer KL, Venter C, Cassin AM, et al. Should wheat, barley, rye, and/or gluten be avoided in a 6-food elimination diet? *J Allergy Clin Immunol*. 2016;137(4):1011-1014.
72. Wilson JM, Platts-Mills TAE. Meat allergy and allergens. *Mol Immunol*. 2018;100:107-112.
73. Simon D, Straumann A, Dahinden C, et al. Frequent sensitization to *Candida albicans* and profilins in adult eosinophilic esophagitis. *Allergy*. 2013;68(7):945-948.
74. Castro Jimenez A, Gomez Torrijos E, Garcia Rodriguez R, et al. Demographic, clinical and allergological characteristics of Eosinophilic Esophagitis in a Spanish central region. *Allergol Immunopathol (Madr)*. 2014;42(5):407-414.
75. Gómez Torrijos E, Sánchez Miranda P, Donado Palencia P, et al. Eosinophilic esophagitis: demographic, clinical, endoscopic, histologic, and atopic characteristics of children and teenagers in a region in central Spain. *J Investig Allergol Clin Immunol*. 2017;27(2):104-110.
76. Philpott H, Dellon E. Histologic improvement after 6 weeks of dietary elimination for eosinophilic esophagitis may be insufficient to determine efficacy. *Asia Pac Allergy*. 2018;8(2):e20.
77. Molina-Infante J, Arias A, Vara-Brenes D, et al. Propofol administration is safe in adult eosinophilic esophagitis patients sensitized to egg, soy, or peanut. *Allergy*. 2014;69(3):388-394.
78. Asserhøj LL, Mosbech H, Krøigaard M, et al. No evidence for contraindications to the use of propofol in adults allergic to egg, soy or peanut. *Br J Anaesth*. 2016;116(1):77-82.
79. Mehta P, Sundaram SS, Furuta GT, et al. Propofol use in pediatric patients with food allergy and eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr*. 2017;64(4):546-549.
80. Buehrer S, Immoos S, Frei M, et al. Evaluation of propofol for repeated prolonged deep sedation in children undergoing proton radiation therapy. *Br J Anaesth*. 2007;99(4):556-560.
81. Brown TM, Leung J. Tolerance of baked cheese in cow's milk-mediated eosinophilic esophagitis. *ACG Case Rep J*. 2019;6(9):e00217.
82. Molina-Infante J, Gonzalez-Cordero PL, Arias A, et al. Update on dietary therapy for eosinophilic esophagitis in children and adults. *Expert Rev Gastroenterol Hepatol*. 2017;11(2):115-123.
83. Carlson DA, Hirano I, Zalewski A, et al. Improvement in esophageal distensibility in response to medical and diet therapy in eosinophilic esophagitis. *Clin Transl Gastroenterol*. 2017;8(10):e119.
84. Rodríguez Almagro J, Hernández Martínez A, Lucendo AJ, et al. Health-related quality of life and determinant factors in celiac disease. A population-based analysis of adult patients in Spain. *Rev Esp Enferm Dig*. 2016;108(4):181-189.
85. Dorn SD, Hernandez L, Minaya MT, et al. The development and validation of a new coeliac disease quality of life survey (CD-QOL). *Aliment Pharmacol Ther*. 2010;31(6):666-675.
86. Johnston SD, Rodgers C, Watson RG. Quality of life in screen-detected and typical coeliac disease and the effect of excluding dietary gluten. *Eur J Gastroenterol Hepatol*. 2004;16(12):1281-1286.
87. Casellas F, Rodrigo L, Lucendo AJ, et al. Benefit on health-related quality of life of adherence to gluten-free diet in adult patients with celiac disease. *Rev Esp Enferm Dig*. 2015;107(4):196-201.
88. Lucendo AJ, Arias-González L, Molina-Infante J, et al. Determinant factors of quality of life in adult patients with eosinophilic esophagitis. *United Eur Gastroenterol J*. 2018;6(1):38-45.