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PEDIATRIC GASTROENTEROLOGY (S ORENSTEIN, SECTION EDITOR)

Meta-Analysis-Based Guidance for Dietary Management in Eosinophilic Esophagitis

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Abstract Eosinophilic esophagitis (EoE) is a prevalent chronic esophageal disorder, triggered and maintained by immunologically mediated responses against dietary antigens. EoE represents the most recent form of food allergy, and its control by avoiding offending foods has increasingly appeared as a therapeutic alternative to achieve and maintain remission. Dietary therapies have proved equally effective in pediatric and adult EoE patients, among whom various types of interventions to eliminate or reduce food antigens exposure have been evaluated. A recent meta-analysis showed elemental diet as the most effective option to induce disease remission, but with a limited application in clinical practice. Inconsistency and wide variability in results from skin allergy testing-directed food restriction contributed to dissatisfaction with implementation of this option, which subsequently was displaced by empiric elimination of common food allergens. Such empiric elimination of common food allergens is now recognized as the best alternative for dietary treatment, with moderate-to-high efficiency and reproducible results. This review provides evidence-based insights into the dietary management of EoE.

Keywords Eosinophilic esophagitis · Food allergy · Food hypersensitivity · Dietary therapy · Elimination diet · Elemental diet · Allergy testing · Six-food elimination diet · Four-food elimination diet

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Introduction

Eosinophilic esophagitis (EoE) represents a prevalent cause of chronic or recurrent esophageal symptoms in European and North American countries [1], and in recent years, it has also emerged as a disorder of increased frequency in other regions such as Central and South America [2–5], Asia [6–8], and North Africa [9, 10].

Since the initial description of the disease in the early 1990s [11], EoE was recognized as particular form of food allergy. During the next decade, the dietary management of EoE patients (mainly children) simply consisted of exclusively feeding them with amino acid-based elemental diets and evaluation of that management was restricted to a handful of studies [12, 13, 14••]. Simultaneously, an expanding range of options for treating EoE was being used by several researchers, ranging from endoscopic dilations aimed to enlarge the esophageal caliber and resolve esophageal strictures, to different drugs that included topic steroids, anti-allergy agents, and even monoclonal antibodies [15].

In recent years, an interest in dietary therapies for EoE has emerged as a result of the limitations associated with other therapies, and the effectiveness of dietary therapy for achieving and maintaining disease remission while avoiding the need for drugs.

Research on the use of dietary therapies to achieve EoE remission was initially carried out in pediatric patients, the group most susceptible to the adverse effects of steroidal anti-inflammatory drugs, especially adrenal suppression [16]. Those studies were subsequently extrapolated to adult patients, for whom data on the efficacy of every treatment option are now available. Recent analysis has systematically reviewed the available body of research on the efficacy of dietary modifications in achieving histological remission of EoE [17••] to provide clinicians with evidence for making

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decisions concerning the complex management of EoE (Fig. 1). The different alternatives for the dietary management of patients with EoE, including its effectiveness, advantages, and limitations, will be reviewed in this paper and advice for its implementation in clinical practice will be provided.

Elemental Diets as Treatment for EoE

Rationale and Efficacy of Elemental Diets

Elemental diets are synthetic food formulations lacking antigenic capacity because in them all proteins and small peptides are eliminated. Nitrogen sources are provided exclusively by individual amino acids, synthesized separately, and mixed in suitable proportions. Carbohydrates, fats, and other micronutrients are formulated to provide all the nutritional needs.

The first evidence on the efficacy of dietary intervention for EoE was provided by Kelly et al. in 1995 [11], who exclusively used an amino acid-based formula to feed a series of ten children with severe esophageal eosinophilia attributed to gastroesophageal reflux and refractory to other therapies: after a minimum of 6 weeks, a complete resolution of disease was seen in eight children, and the remaining two had symptomatic improvement with a significant reduction in the eosinophilic infiltrate. The high efficacy of elemental formulas has been repeatedly confirmed in subsequent reports in children and adolescents with EoE [12, 13, 14••, 18•, 19••, 20], as well as very recently in adults [21•]: Peterson et al. prospectively enrolled 29 adult EoE patients to follow an exclusive elemental diet for 4 weeks. Out of the 18 subjects who completed the study, 13 achieved complete histological response (defined as <10 eosinophils per high-power field [hpf]), and 4 more achieved a reduction of 50 % of the peak eosinophil density at baseline. According to per protocol analysis, the overall efficacy was 94.4 % in terms of histological remission, but it was reduced to only 58.6 % in the intention-to-treat analysis due to difficulties in adherence to the diet.

Despite the fact that no controlled clinical trials exist, a recent meta-analysis has shown that the overall effectiveness of elemental diet in inducing histological remission of EoE (i.e., a reduction in peak eosinophil counts to <15 per hpf) was 90.8 % (95 % CI, 84.7–95.5 %) [17••].

Disadvantages and Limitations of Elemental Diets

Although elemental diets have been demonstrated to outperform, in terms of efficacy in inducing histological remission in EoE [22], all other dietary treatments as well as treatment with topic steroids, their use in clinical practice is limited due to their many disadvantages that severely impact treatment adherence [21•]. These include the psychological and social effects of complete avoidance of all kinds of table foods, the awful taste of elemental formulas (a fact that mandated feeding 80 % of pediatric patients in some series via a nasogastric tube [12]), and their high costs not universally covered by health insurances.

In the long term, elemental diets do not represent a proper nutritional alternative for a chronic disease like EoE, and the only realistic utility of this diet in clinical practice is restricted to small children who are not yet taking solid food, and to patients who could tolerate the dietary restrictions involved in an exclusive elemental diet, but only for the period of time required for identifying specific food triggers for EoE through food reintroduction [23] (Table 1). Also, we should keep in mind that young children who have no need to chew because of an exclusively liquid elemental diet might not adequately develop facial muscles and may therefore have delayed

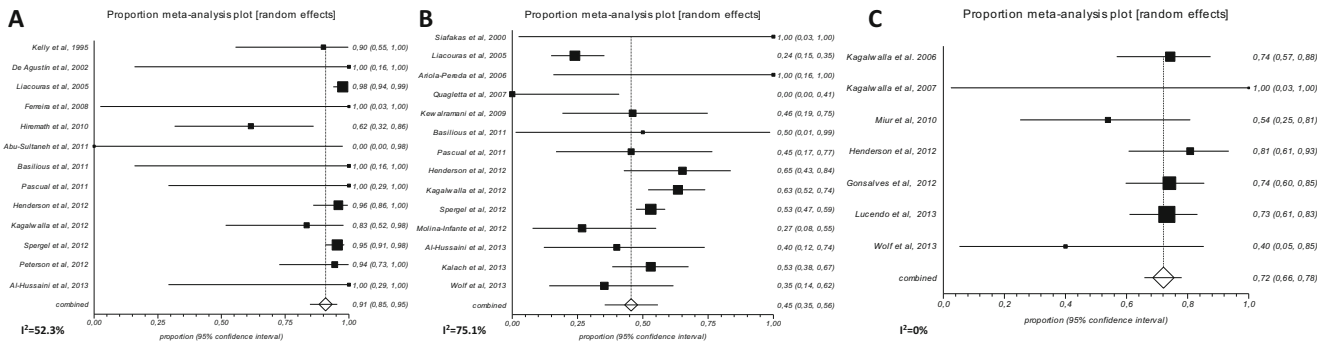

Fig. 1 Summarized effects of elemental diets (**a**), skin allergy testing-directed food removal (**b**), and empirical six-food elimination diets (SFED, **c**) for inducing histologic remission of EoE, according to a recent meta-analysis [17••]. Confidence intervals at 95 % were calculated using the exact binomial method. I^2 values indicate the heterogeneity or intra-study differences. It can be seen that the higher efficacy rate was for elemental diets (91 %), followed to SFED, which showed a combined response rate of 72 %, extremely homogeneous among the individual studies considered (I^2=0 %). Skin allergy testing-directed food removal showed the lowest combined effectiveness (45 %) with a wide heterogeneity of results from individual studies

Table 1 Comparative advantages and drawbacks of the major available food treatment alternatives for EoE

Elemental diet	
Advantages	Limitations
Highest effectiveness	Unpleasant taste, table food must be avoided
Fast response time	Often, gastric tube administration in children
Easy instructions	High cost of elemental formula
Minor risk of dietary contamination	Poor adherance
Allergy testing not needed	Long-term use results inconvenient
	Long-term use in younger children may delay facial muscle development and speech
Skin allergy testing-directed elimination diet	
Advantages	Limitations
Ability to remove fewer foods from patients' diets	High variability in response rates
Exclusive removal of specific foods	Low sensitivity and specificity of allergy testing
Rapid normalization of diets	Low standardization for atopy patch testing
Moderate efficacy	Possible dietary contamination
Empiric elimination diets	
Advantages	Limitations
Exclusive removal of the most common antigens	Possible dietary contamination
Allergy testing not needed	Lack of standardization of protocol
Moderately high efficacy	The adequacy of diets to local customs should be assessed
Rapid normalization of diet	Difficulties in reading/interpreting food labeling
Favourable cost-effectiveness compared to topical steroids	

In addition to those presented in the table, all dietary interventions share the common inconvenience of a need for repeated endoscopic and bioptic assessment during food reintroduction challenge in order to identify specific food triggers; they also share the common advantage of the possibility of prolonged drug-free remission of the disease

speech development [24], which also limits the time of using this dietary alternative.

Allergy Test-Driven Food Elimination

Origin and Rationale

The repeated demonstration that EoE was a specific form of food allergy, which went into remission after avoiding exposure to foods, led researchers (mainly allergists) to try to identify the food responsible for the disease through clinical history (which is complicated, as patients generally do not associate the onset of symptoms with consumption of specific foods), but especially by skin allergy tests, including both skin prick tests (SPTs) and atopy patch tests (APTs). Using this methodology to identify specific foods to exclude was thought to be able to achieve similar results to using elemental diets, but added convenience, feasibility, and quality of life for patients by allowing them to consume an almost normal diet.

In 2002, Jonathan Spergel, an allergist from Philadelphia (Pennsylvania), used for the first time a combination of SPTs and APTs in order to identify the food(s) responsible for EoE in a series of children [25]. Avoiding those foods that produced positive results on skin testing produced clinical and histological remission in 49 % of treated patients [26], while excluding an average of 5 foods in each child's diet.

Efficacy of Skin Allergy Test-Driven Food Elimination for EoE in Children and Adults

Preliminary results of the aforementioned study were subsequently updated by the authors in later publications [18•, 19••, 20, 21•, 22–27]. The latest work, published in 2012, summarized the group's previous experience with the elimination of foods directed by skin tests, with an overall efficiency of 53 % [18•]. The sensitivity and specificity of allergy skin testing was very variable, with less than 10 % of positive results concordant in both SPTs and ATPs. The sensitivity of the tests for cow's milk, the main food triggering EoE, which will be discussed below, was extremely low. The strategy of empirically eliminating cow's milk, along with foods with positive skin allergy test results, from the diet achieved remission rates of up to 77 % [18•]. However, this approach is not strictly based on skin allergy tests.

Although the diagnostic accuracy of skin allergy tests is insufficient to design effective diets for EoE patients, as was early recognized in clinical guidelines [1], other authors have

used the strategy of excluding food with positive skin test results to induce remission of EoE. In pediatric patients, Henderson et al. documented remission in 65 % (15/23) of children who followed this diet, with average reduction in the peak of eosinophil density in the esophageal inflammatory infiltrate from 38 to 7 cells/hpf [19••]. Similarly, Kagalwalla documented remission in 63 % (52/82) of children with EoE who followed the same strategy [28]. In contrast, other studies have shown a significantly lower remission rate: Liacouras only documented remission in 24 % (18/75) of pediatric patients [12], and even other researchers have documented only a partial histological response in less than half of children, with the peak in eosinophil count above 15 cells/hpf after restricting those foods with a positive skin test result [29, 30].

As in the case of elemental diets, studies on the usefulness of skin allergy tests in adult EoE patients are more limited than in pediatric EoE patients. The best documented research to date was conducted by Molina-Infante et al. who excluded from the diet all foods that had a positive result in SPTs, APTs, and prick–prick tests (PPT). Remission was only achieved in 4 of the 15 subjects studied (26 %) [31••]. A second study exclusively involving adults could only report symptomatic improvement in one of the 6 patients recruited, without any reaching histological remission [32].

The variable efficacy of food removal based on allergy skin tests in EoE has recently been analyzed in a systematic review: the remission rate achieved after this strategy was only 45.5 % (95 % CI, 35.4–55.7 %) with wide heterogeneity in the results [17••] and was significantly lower for adults compared to children (32.2 *vs.* 47.9 %).

Specific Serum IgE-Driven Elimination Diets in EoE

Patients with EoE are usually sensitized to several foods and aeroallergens, as demonstrated by skin allergy test results and also by higher values of serum food-specific IgE, compared to controls. After the repeated documentation of the very limited utility of serum food-specific IgE in the management of EoE patients [33, 34], the potential utility of measuring specific IgE against single allergen molecules by using microarray assay-based component-resolved diagnosis (CRD) has been recently assessed for tailoring specific dietary management of EoE [35, 36•]. Although preliminary data suggested a potential beneficial effect [35], a recent prospective study failed to demonstrate effectiveness of CRD-based dietary treatment in EoE patients [36•], as a reflection of the limited relevance of IgE in the pathophysiology of the disease.

Limitations of Allergy Tests in the Treatment of EoE

The limitations in the effectiveness of diets designed from IgE-based allergy testing activity, namely PPTs and SPTs, to control EoE have been repeatedly reported. In parallel, a growing body of evidence questioned the involvement of IgE-mediated reactions in the origin of EoE and the increasing recognition that EoE could represent a disease mainly restricted to the esophagus with a very limited systemic manifestations. Thus, serum IgE levels do not correlate with clinical or histopathological activity of the disease and food-specific IgE levels have repeatedly shown a very limited sensitivity and specificity of around 50 % in identifying the foods responsible of EoE [33, 34, 37••, 38••]. Exposure to foods that trigger EoE rarely cause anaphylaxis [39]; and although local synthesis of IgE have been demonstrated within the esophageal mucosa of children with EoE, independently of their displaying other forms of atopy [40], this IgE seems not to mediate immediate immune reactions. Furthermore, mast cells (which are an abundant cell type in the inflammatory infiltrate of EoE patients that usually are activated by IgE) show no significant differences in density or activity among patients with atopic and non-atopic EoE [41].

Relevant evidence against a prominent role for IgE in the pathophysiology of EoE is provided by the fact that treatment with monoclonal antibodies blocking IgE (omalizumab) repeatedly has been found ineffective in improving EoE in children and adults, accordingly to observational studies and a recent clinical trial [42, 43, 44•].

However, it is still possible that IgE may play a limited role in the early stages of the development of EoE, especially in younger patients: the immaturity of the digestive enzyme system and the intestinal mucosal barrier in younger children favors the absorption of partially digested peptides from the diet. This would stimulate Th2-type reactions, with cytokine secretion and IgE production [45]. Because this process decreases with age, the role of IgE in older patients would also progressively decrease. In fact, EoE has recently been recognized as an IgG4-associated disorder, instead of an IgE mediated disease [44•] after a dense infiltration by IgG4 positive plasma cells were demonstrated located around the vessels of the lamina propria of adult EoE patients.

Empiric Elimination of Common Dietary Antigens as a Treatment Option for EoE

Rationale and Efficacy of Six-Food Elimination Diets

In an attempt to overcome the many disadvantages associated with exclusively feeding patients with elemental formulas and the low sensitivity and specificity of skin allergy tests to identify the food(s) responsible for EoE, Amir Kagalwalla, a pediatrician from Chicago, explored in 2006 an alternative treatment consisting of removing from the diet the six kinds of foods most often related to food allergy in children [14••]: After removing milk protein, wheat, eggs, soy, peanuts/tree nuts, and fish/seafood from the diets of 35 children for a 6-

week period, a resolution of the eosinophilic infiltration (defined as a reduction to <10 cells/hpf) in esophageal biopsies was documented in 26 patients (74 %) and a partial remission (<20 eosinophils /hpf) in three others.

Comparable responses were subsequently reproduced in other retrospective studies in children [19••], and especially in two large prospective studies involving adult EoE patients [37••, 38••]. In parallel, the diet originally used by Kagalwalla was modified slightly to also exclude those foods with SPT positive [19••, 38••] and taking into account geographical differences in patterns of sensitization [37••]. The overall effectiveness of empiric six-food elimination diets (SFED) to induce remission of eosinophilic infiltration in EoE below the diagnostic threshold was 72 % (95 % CI, 66–78 %), according to a recent meta-analysis of 7 studies including 75 children and 122 adults treated [17••]. Notably, the results of the various studies have shown a high concordance in the remission rate (with an heterogeneity (I^2 statistic) of 0 % in the aforementioned meta-analysis). The lack of variability compared with the removal of food driven by skin testing and the improved tolerance by patients compared to elemental diets make these empirical elimination diets the most recommendable dietary treatment approach in the initial management of EoE patients [17••, 24].

However, the removal of 6 types of foods to achieve remission of EoE must be only taken as a first step in the treatment of patients with the disease, to be followed in all cases by a subsequent progressive food reintroduction to identify the specific food(s) responsible for the disease.

Identification of Specific Food Triggers for EoE Through Sequential Single-Food Reintroduction

All dietary treatment strategies are intended to induce EoE remission, as a reference point for subsequent identification of potential food triggers. The goal is to exclude from the diet only the specific food(s) responsible for triggering and maintaining the disease in each individual patient.

In addition to expanding patients' diets by allowing them to consume foods previously excluded, sequential reintroduction of food in EoE, once remission of eosinophilic inflammation is achieved, actually allows identification of the main foods responsible for EoE and how often each food type determines this disease in children [46••] and adults [37••, 38••]. Consuming a previously excluded food after obtaining histological remission of EoE constitutes a food challenge test, which represents the gold standard for the diagnosis of food allergies. Disease monitoring by using repeated endoscopies and biopsies of the esophageal mucosa allows determination of whether the inflammation that characterizes EoE relapses after food challenges and accurately identifies whether a particular food triggers EoE, and if so, to restrict it from the patient's diet indefinitely. Endoscopies with systematically performed biopsies are thus considered necessary to identify with certainty whether a food is triggering EoE and should be removed from the diet, or is well tolerated and can be consumed regularly. The dissociation between clinical symptoms and histology in EoE has been repeatedly documented [47], implying that the absence of symptoms does not mean disease remission in all cases. The implication that long-term food restriction has, in controlling a chronic and progressive disease, such as EoE, and the absence of non-invasive markers to predict the presence or absence of eosinophilic inflammation of the organ [48, 49], led most authors to obtain endoscopic biopsies after reintroduction of individual foods [37••, 46••, 50]; the acceptance of this strategy by patients is largely conditioned on providing sedation during endoscopic exams and the commitment to performing them in defined time frames after food reintroduction.

The several studies available on food reintroduction in EoE have displayed very consistent results, with milk, wheat, and egg as the main foods responsible for the disease in up to 50 % of cases, and no differences between children and adults, or between European and North American research. Common nutritional habits, derived from a similar agricultural and culinary culture, explain these similarities. Other foods have shown different frequencies between studies from different geographical regions, which has been explained by differences in food consumption patterns and sensitization profiles between Spain and the USA, for example. Table 2 presents the relative frequencies with which each EoE food trigger has been identified in different studies.

The number of foods responsible for triggering and maintaining EoE has varied little among different studies, with a usual number between 1 and 3 in each patient [37••, 50, 52]. The fact that the studies in the USA did not completely reintroduce all foods previously excluded [38••], or that once identified, the first food responsible for EoE the study did not continue in the case of children [46••], prevents comparisons with the results of European studies.

Other Varieties of Empiric Food Elimination Diets for Treating EoE

Empiric Cow's Milk Elimination

Cow's milk has been repeatedly shown as the most frequent food associated with EoE in children [18•, 19••, 46••] and adults [37••, 50], becoming involved in the origin of the disease in up to half of patients. Consequently, a retrospective study evaluated the effectiveness of the exclusive restriction of cow's milk in 17 children with EoE, reporting that up to 65 % of them had histological remission of the disease (esophageal biopsies with <15 eosinophils/hpf) and symptomatic improvement [28]. The unexpectedly high efficiency of this strategy could have been influenced by the selection criteria for

Table 2 Frequencies of identification of major food allergens as triggers of EoE in published studies

	Kagalwalla et al. [46••] (Chicago, IL)	Gonsalves et al. [38••] (Chicago, IL)	Lucendo et al. [37••] (Spain)	Molina-Infante et al. [50] (Spain)	Wolf et al. [51] (Chapel Hill, NC)	Kagalwalla et al. [52] (Chicago, IL)
Milk	74 %	50 %	62 %	50 %	44 %	68 %
Wheat	26 %	60 %	28 %	31 %	22 %	16 %
Egg	17 %	5 %	26 %	36 %	44 %	26 %
Legumes	–	–	24 %	18 %	11 %	–
Soy	10 %	10 %	14 %	–	–	21 %
Nuts	6 %	10 %	17 %	–	11 %	–
Fish/seafood	0 %	0 %	19 %	–	11 %	–
Rice	–	–	19 %	–	–	–
Corn	–	–	19 %	–	–	–

patients who were prescribed the exclusive restriction of milk, as having included patients with a previous IgE-mediated allergy to milk protein who underwent to desensitization, an strategy that has been proven as a *cause* of EoE in up to 2.7 % of cases, according to a recent meta-analysis [53]. The results of a recent comparative study showing that eliminating milk from the diet resolved the histological findings in 64 % of EoE patients [54] were not evaluable, as all patients were also treated with PPIs, a strategy that by itself is capable of solving the esophageal inflammation in up to 1/3 of patients with EoE [55].

Empiric Four-Food Elimination Diet (FFED)

The fact that one only one or two foods have been identified as responsible for the EoE in most (between 65 and 85 %) children and adults with this condition indicates that the restriction of a long list of foods and subsequent sequential reintroduction may be unnecessary in many cases. In this regard, a recent Spanish multicenter study evaluated the efficacy of the empiric elimination of the four foods most frequently associated with the development and maintenance of EoE (wheat, milk, eggs, and legumes including soybeans) [50]. Clinical and histological remission was achieved in 28 of the 52 adult patients enrolled (54 %); a significant proportion of non-responders to the FFED (31 %) showed disease remission after following an empiric SFED, resulting in an overall efficacy of the diet of 72 % (the same expected for an empiric SFED). A second prospective multicenter study from USA, published as an abstract, demonstrated histologic remission (defined as <15 eosinophils/hpf) in 39/55 (71 %) of children undergoing a FFED [52].

The advantages of this new strategy of phasing out foods include a less restrictive diet, and therefore, a better acceptance by patients; a shortening of the study time needed to identify the food(s) responsible for EoE; and fewer endoscopies required in most patients.

Sustained Efficacy of Food Trigger Exclusion in EoE

The sustained efficacy of avoiding consumption of food responsible of EoE has been assessed by only two studies conducted in adults [37••, 56]; according to them, all patients who did not take the food(s) responsible remained asymptomatic and with histologic remission in esophageal biopsies for a period of up to 3 years, making drug treatment not needed.

With regard to the possibility of inducing tolerance to foods responsible for EoE after a period of prolonged avoidance of consumption, the limited information on this aspect is daunting, because the disease recurred in all cases following food reintroduction, even after remission for up to a 4-year period [46••].

Dietary Treatment for EoE: Keys to Success

Despite the fact that SFED proved more cost-effective than topical steroids as a first-line treatment for EoE, according to a recent cost-utility analysis [57], dietary treatment represents a greater challenge for the patient than for his/her doctor. It usually requires a special effort in identifying food allergens included in multiple dishes and processed foods, especially challenging when eating socially and food labels are not available, a careful reading of food labels and lists of components and imaginative solutions to meet the restrictions of the diet with food choices allowed. It is therefore imperative that dietary treatment should be offered to EoE patients (or their parents) who have a high motivation, as well as a cultural and intellectual level adequate to interpret and solve the many limitations that come from an increasingly industrialized world where most food products are brought to consumers after some processing. Effective avoidance of unpermitted foods depends on the proper identification of obvious sources of allergens and food components, such as those hidden behind confusing terms on the labeling of processed products.

Dietary interventions in EoE patients go beyond the purely therapeutic aspect and should be simultaneously considered as diagnostic methods for the food causes of the disease, while its implementation in the medium- and long-term should be guaranteed. Dietary treatment has been understood as a succession of three main stages, along which the targets vary in parallel with the diet followed by the patient [58]:

Remission Phase During the minimum 6 weeks that it should take, the maximum number of foods is simultaneously removed from the patient's diet. It is important to note that this very restrictive diet is not final, but a temporary method of study; therefore, the patient will be asked for a maximum adherence to the diet because if he/she does not respond, the opportunity to follow a drug-free treatment will be lost. Supplementation with elemental formulas may be occasionally needed to ensure an adequate supply of basic nutrients, especially in younger patients [37••]. After this period, an endoscopy with biopsies under sedation must be scheduled.

Food Reintroduction Phase This phase will be performed in patients showing histological remission, and it has the dual purpose of identifying the specific food triggering EoE in a given patient by using a food challenge test (which, as said before, constitutes the gold standard for studying food allergy), while enabling an increasingly wide and varied diet. Those foods previously excluded are individually and progressively reintroduced, and patients should be advised of the convenience of its regular and daily intake, and not occasionally. A "wash out period" after the demonstration of esophageal inflammation and prior to the reintroduction of a new food does not seem necessary.

Different authors have followed a variable order for reintroducing the different foods previously excluded; this does not affect the identification of the food causing EoE, but might determine the adherence to the diet. Some authors have recommended reintroducing first those foods least likely to trigger EoE, claiming that this strategy allowed rapid increase in the variety of food consumed [18•, 59]. By contrast, other authors recommend starting by reintroducing wheat and milk first, as despite the fact that both are the most often foods involved in EoE [37••, 50], the impact on the normalization of a patient's diet if they are tolerated is very significant.

Our recommendation is to perform an endoscopic assessment with biopsies 6 weeks after the reintroduction of every single food, a period that may be shortened in case of occurrence of obvious symptoms in a previously asymptomatic patient. Some authors have made endoscopy after the reintroduction of two foods [38••], a strategy that may not be appropriate, as it is well described that the absence of symptoms in a patient with EoE does not imply the absence of esophageal eosinophilic inflammation [47]. Since the identification of a particular food as a causing EoE will implicate a long-term avoidance in the diet, this causal relationship should be well documented.

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

Nutritional Limitations of Elimination Diets

Some authors have recommended the involvement of a dietitian or nutritionist in the dietary management of patients with EoE as a determinant of its success [58]. However, experiences from adult patients undergoing empiric elimination diets have repeatedly demonstrated that the participation of these professionals, although desirable, is not essential to achieve high rates of success in the management of the disease [37••, 50], as patients can be adequately handled by gastroenterologists if specific guidance is provided.

In fact, empirical SFED allows especially free consumption of high nutritional value foods, such as meat (all type), fruits, and vegetables. Thus, the supply of proteins with a high biological value, carbohydrates, fiber, minerals and vitamins is guaranteed. A SFED is usually monotonous and repetitive, but never nutritionally inadequate. Although some weight loss has been documented at the beginning of the diet (with a maximum of 7 kg documented in the case of adult patients) [37••], this loss has been mainly associated with restricting the intake of some foods containing milk, wheat, and eggs

(including pasta, sweets, and pastries among them) than with a real nutritional deficit.

The involvement of a nutritionist or dietician can be better justified in the case of young children, especially if they already have a baseline nutritional deficit. Prolonged food restrictions should be monitored, and the order of food reintroduction properly programmed in order to avoid long periods without supply of dairy and cereals if possible.

Dietary Advice for EoE Patients During Elimination Diets

The design of new schemes of empirical elimination diets for managing EoE must rely on food and culinary standards of the population in which they are applied, as well as the population's food allergy profile. It is well documented that different environmental exposure patterns determine different frequencies of sensitization throughout different populations [60]. Diets of children and adults also differ [61], a fact that should be considered.

Whenever possible, fresh and unprocessed products (fruits, vegetables, and meat) should be consumed, and cooking at home is preferred to restaurants and industrially processed products. Processed meats (sausages and burgers) should be avoided, as should meats cooked in sauces and creams. Attention should be paid to the products that have been prepared in oil that was previously used for frying foods containing wheat or egg.

Industrial breads, like rolls and pastries, often contain milk and occasionally egg that are used as emulsifiers; therefore, bread must be purchased in a traditional bakery or elaborated at home.

It is highly recommended to provide patients with written instructions to help them in identifying allowed and forbidden foods (which also vary along the sequential food reintroduction process), as well as lists of terms that make identifying hidden allergens or food components easier. Lists with names or trademarks of products to consume or avoid can also be provided, as well as proposals of menus that facilitate an appropriate diet for the patient.

Management of Patients who do not Respond to Empirical Six-Food Elimination Diets

Although empiric SFED provides a high rate of remission, up to 30 % of patients are non-responders to the diet, so the disease persists among them. Once relapsed because of poor adherence to the diet, or accidental or inadvertent consumption, testing an exclusive elemental diet is not an appropriate option for these non-responder patients, because the maintenance of remission in the long-term does not seem realistic, despite the fact that a good proportion of patients could achieve disease remission if they were compliant with the diet.

In fact, in the case of a patient with EoE and failure to remit during a SFED (including all kinds of cereals, dairy products, eggs, vegetables, soy, seafood, and nuts), but who achieved disease remission after exclusively feeding with an elemental formula, offending foods would reasonably be meats and/or plant foods. Meats have generally little allergenic capacity, and most of its proteins are denatured during cooking; plant foods (fruits and vegetables) contain panallergens including profilins or lipid transfer proteins (LTP) [62], which are widespread for many species, so they could hardly be restricted from a diet without excluding a wide range of essential nutrients.

Patients who do not respond to dietary treatment are candidates for drug treatment based on topical steroids. Looking ahead, it is a requisite the development of precise techniques to know the individual allergens that determine EoE in each particular patient. Meanwhile, empiric elimination diets and food reintroduction challenges constitute the best alternatives for the dietary management of EoE.

Conclusion

Dietary therapy is an effective treatment option to achieve and maintain a drug-free disease remission that should be offered to both children and adults with EoE. Cumulative evidence supports the implementation of dietary therapy in clinical practice, especially for motivated patients and families, considering patients' preferences and available resources. Empiric elimination diets, based on restricting from the diet the foods with a higher allergenic capacity, have been consistently shown as superior to exclusive elemental formulas and allergy test-directed food elimination, and should be now considered the most appropriate dietary intervention. After achieving histopathological remission, sequential food reintroduction allows the identification of specific food triggers by documenting disease recurrence, while enabling an increasingly wide and varied diet. Only one or two foods are identified as responsible of EoE in most of patients, and avoiding its consumption leads to prolonged disease remission. Less restrictive empirical dietary elimination schemes should be investigated in order to provide patients with easier to follow, faster, cheaper, and less inconvenient effective dietary therapies.

Compliance with Ethics Guidelines

Conflict of Interest Alfredo J. Lucendo declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently have been highlighted as:
• Of importance
•• Of major importance

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