Food Allergy (M Fernández-Rivas, Section Editor)

Dietary Management of Patients with Eosinophilic Esophagitis

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Opinion statement

Twenty years after it was first described, eosinophilic esophagitis (EoE) is now recognized as a prevalent disorder, representing the second most common cause of chronic esophagitis (after gastroesophageal reflux) and constituting the main cause of esophageal symptoms in young patients. In most cases the disease is triggered and maintained by exposure to food antigens, thus representing a novel form of food allergy. While topical steroids still constitute the prevailing therapeutic option, there is increased interest in dietary therapy as a treatment alternative capable of inducing and maintaining drug-free remission of the disease. First assessed in a pediatric series, more recent studies have demonstrated that dietary therapy is equally effective for adult sufferers of EoE. Indeed, various types of dietary interventions that either eliminate or reduce food antigens from the diet have been shown to induce remission of esophageal inflammation and its derived symptoms in a high proportion of patients. After remission has been achieved, food reintroduction is an essential part of the dietary management of EoE and should always be considered once esophageal biopsies are normal. Food reintroduction consists of a food allergy challenge that facilitates the identification of specific food triggers for the disease. This allows patients to follow as normal a diet as possible, thus improving the acceptance of and adherence to specific dietary restrictions. The dietary management of EoE is a challenging therapy that should be considered for every patient with the disease. Its major limitations arise from the necessity of repeated endoscopies with biopsies during the food reintroduction protocol, as well as from the absence of noninvasive subrogated markers of disease activity. For these reasons, the use of dietary therapy has been limited to highly motivated patients who are reluctant to utilize drug-based therapies on a chronic basis, as well as to highly motivated health-care providers. Ongoing research on less restrictive dietary options should facilitate the spread of dietary interventions, making this type of therapy more available for extended use.

Introduction

Eosinophilic esophagitis (EoE) represents an emerging gastrointestinal disorder characterized by symptoms of esophageal dysfunction, including dysphagia and food impaction, along with marked esophageal eosinophilia in mucosal biopsies, both of which persist after treatment for acid gastroesophageal reflux [1]. First defined 20 years ago as a distinctive clinico-pathological syndrome [2], EoE currently represents an emerging chronic disease that usually persists from childhood into adulthood [3•, 4], with an estimated prevalence of 43-56 cases/100,000 inhabitants in both America and Europe, affecting both children and adults [5–8].

EoE has been related to allergies since its first descriptions. In fact, pediatric and adult patients commonly present a family or personal allergic background, including asthma, rhinitis, conjunctivitis, or eczema with variable frequency [1]. Moreover, peripheral eosinophilia is present in 50 % of patients, with three out of four exhibiting elevated serum IgE levels [9]. Food and aeroallergen sensitization are also common, as determined by means of positive skin prick tests (SPTs) in patients of all ages [10-12]. However, the definitive definition of EoE as a characteristic manifestation of food allergy only came after disease remission was achieved by feeding a series of pediatric patients exclusively with an amino acid-based elemental formula [13]. In this groundbreaking study, the disease recurred in all cases once patients resumed a normal

diet, demonstrating unequivocally for the first time that food allergy plays a causal role in chronic esophagitis, while simultaneously establishing a gold standard for comparing subsequent therapies.

However, despite the great number of studies carried out on the disease over the past 20 years, management of EoE remains controversial. Current treatments include the use of swallowed steroids with a topical effect, various dietary modifications, and endoscopic dilation. Even more recently, several monoclonal antibodies have been assayed [14]. With all this, a commonly accepted algorithm for treating patients is still lacking, mostly due to limited information regarding the long-term effects of different therapies in modifying the natural history of the disease and its associated subepithelial fibrosis [14, 15° , 16°]. As a result, there is a wide variability in both the standard of care for EoE patients and the adherence to proposed international guidelines in clinical practice [6, 17°].

An increasing body of knowledge has recently renewed interest in the dietary management of EoE as a drug-free alternative to topical steroids, which still constitute the most widely utilized medical treatment for EoE in patients of all ages. This article aims to review all available dietary approaches for the management of EoE, along with the advantages and limitations of each, in order to provide practical advice for the successful management of EoE through diet.

Treatment

 The natural history of EoE is starting to become more clearly defined, mainly through longitudinal studies focused on determining the evolution of the untreated disease. We know that, in the absence of treatment, EoE tends to persist over time, with chronic symptoms and inflammation significantly affecting health-related quality of life (QoL) [3•], but usually with no impact on the nutritional state of the patient [18]. Characteristic endoscopic features in children include acute inflammation, especially mucosal edema, along with whitish exudates and linear furrows [19]; adult patients additionally present with fibrotic changes, such as rings and strictures [20]. However, no malignant potential has been associated with EoE until now [18]. Moreover, retrospective studies have demonstrated that the duration of untreated disease directly correlates with the prevalence of esophageal strictures in a time-dependent manner [21•]. Likewise, an association has been demonstrated in the natural history of Crohn's disease.

The classical treatment goals of EoE, namely (1) the resolution of clinical symptoms and (2) achieving and maintaining disease remission, have been expanded to include (3) the prevention of fibrotic complications such as strictures, (4) avoidance of the iatrogenic effects of medication, (5) maintenance of an adequate QoL, and (6) the prevention of nutritional deficiencies due to dietary treatment.

Summary of available alternatives to dietary therapy for EoE

- Pharmacological treatment for EoE patients has mainly comprised the use of several anti-inflammatory drugs used in other allergic disorders. The first reported cases of EoE were effectively managed with systemic steroids, which were later replaced by topical steroids after these were shown to have a similar effectiveness with a lower rate of side effects. First used in pediatric patients [22], topicallyadministered swallowed fluticasone propionate (FP) has been shown to be highly effective in children [23], significantly superior to a placebo [24] and comparable to oral prednisone [25] (1b, grade A). Similar results have been documented in adults [26]. Viscous budesonide has also emerged as an alternative treatment for both children [27] and adults with EoE [28], having been proven safe and effective (1b, grade A). Ciclesonide has also recently been added to the pharmacological armory for treating EoE [29]. However, given the chronic nature of EoE, sustained treatment with steroids or repeated courses must be considered, even after achieving disease remission. Finally, azathioprine/ 6 mercaptopurine was found to be effective in causing the remission of symptoms and eosinophilic infiltration for periods of 3-8 years in adults with steroid-dependent EoE and eosinophilic gastroenteritis with esophageal involvement [30].
- Other anti-allergy drugs such as anti-H1 blockers or the mast cell stabilizer disodium cromoglycate have shown no therapeutic benefit in patients with EoE [31]. Montelukast is likewise not recommended for the management of EoE [1], as it is unable to maintain remission achieved with topical steroids [32] (4, grade C).
- Several biological therapies based on monoclonal antibodies have been assessed in EoE with limited results. Thus, the anti-TNF-α infliximab failed to demonstrate any beneficial effects in adult EoE patients [33], nor did the anti-IgE omalizumab lead to clinical improvement in children [34]. However, when the anti-IL-5 monoclo-

nal antibodies mepolizumab and reslizumab were analyzed in randomized, controlled trials in both adult [35] and pediatric [36, 37] patients, tissue eosinophils were significantly reduced. Unfortunately, clinical improvement was minimal. (1b, grade A).

- Despite the fact that EoE is defined as the persistence of eosinophilic inflammation after acid suppression, proton pump inhibitors (PPIs) have been used successfully as a sole therapy for EoE patients [38, 39]. The anti-inflammatory properties of PPIs were recently demonstrated in vitro after they were able to reduce the gene expression of eotaxin-3 (a key chemo-attractant involved in the pathophysiology of the disease) in esophageal cell cultures from EoE patients [40]. Until a clearer elucidation of the real significance of PPI-responsive EoE is developed, consensus guidelines currently consider this disease to be a specific manifestation of gastroesophageal reflux disease [1].
- Endoscopic dilation, a mechanical procedure with no effect on the underlying inflammatory process, seems to result in at least a short-term improvement of symptoms in the majority of patients, according to a recent meta-analysis [41]. It has mostly been used in adult EoE patients, who often present esophageal stenosis with a reduction of esophageal caliber. When performed by an experienced specialist, esophageal dilation is a safe procedure [41]. However, various risk factors for complications have been identified, including a long evolution of dysphagia, high eosinophil density, young patient age, repeated procedures, and luminal narrowing in the upper and middle esophageal thirds [42, 43].

Dietary approaches for EoE

Elemental diet in EoE

- Since 1995, after an initial report showed that feeding 10 children exclusively with an amino acid-based elemental formula led to symptom relief and histological normalization of EoE [13], several studies have reproduced these findings in pediatric series [44, 45••, 46••]. In fact, results show that more than 90 % of patients rapidly reach peak eosinophil counts <15/hpf, with symptomatic improvement in >96 % of cases (4, grade C). Moreover, subsequent controlled re-introduction of solid foods results in recurrence of gastrointestinal symptoms specific to individual "trigger" foods.
- The first report regarding the use of elemental diet to treat adult EoE has been published only very recently [47••]. A series of 29 patients were prospectively recruited and told to avoid any kind of food except an elemental formula for a four-week period. Three patients abandoned the study protocol on the first day and eight more consumed forbidden solid foods during the first 2 weeks of the study period. A pathological infiltration of >15 eos/hpf persisted in only one out of the 18 adults who completed the study (4, grade C), giving a per-protocol efficacy of 94.4 %, which went down to 58.8 % when analyzed for intention-to treat.

- A rapid recurrence of eosinophilic inflammation after resuming a normal diet is the norm in both children and adults; therefore, additional dietary strategies should be implemented after elemental diet-induced remission of the disease.
- Although the efficacy of an elemental diet has proven superior to that of any other type of dietary intervention in managing EoE, several drawbacks restrict its use in clinical practice, including its unpleasant taste (which forces up to 80 % of pediatric patients to be fed through a nasogastric tube [31]), its high non-adherence rates [48], the many limitations it places on social activities due to the complete avoidance of any kind of table food, and its high cost. This latter limitation leads to the additional disadvantage that some insurance plans do not cover this type of therapy.
- The only realistic utility of elemental diet in clinical practice is to feed infants and toddlers, among whom the restriction of having no additional food may be better tolerated, and only during the length of time required for food reintroduction with the goal of identifying specific dietary triggers.

Elimination diets directed by allergy testing

- The growing body of evidence showing that exposure to food allergens leads to EoE has prompted researchers to attempt to identify specific food triggers for the disease, sometimes using clinical histories (which is complicated as patients do not usually associate the consumption of certain foods with the appearance of symptoms), but most often using skin prick tests (SPTs) and/or atopy patch tests (APTs).
- In 2002, Spergel et al. used SPTs and APTs on pediatric EoE patients for the first time to determine a suitable elimination diet [49]. The avoidance of foods that gave positive skin test results led to histological and clinical resolution in 49 % of patients [50•]; with this strategy, an average of five foods were excluded from each child's diet (4, grade C). The authors adverted on the variable sensitivity and specificity of these allergy tests, with <10 % of positive results in both tests, along with their low sensitivity to cow's milk, which, as noted below, is the most common food trigger for EoE. The same authors have recently evaluated a new strategy consisting of the elimination from the diet of foods identified through SPT/APT, in addition to an empirical elimination diet. Combining the two strategies led to increases in histological remission rates of up to 77 % [50•].
- Unfortunately, the aforementioned results regarding the histological remission of EoE have not been reproduced by other research groups. Allergy tests failed to identify food triggers in most patients in several pediatric [51•, 52, 53] and adult series [47••, 54••, 55, 56•, 57••]. Moreover, food-specific IgE serum measurements and SPTs were

neither sensitive nor specific methods for predicting EoE triggers in adult patients [57••, 58••].

A growing body of evidence points to the involvement of a cellmediated delayed reaction against foods rather than an IgE-mediated reaction in the pathophysiology of EoE. As a result, EoE usually coexists together with other IgE-mediated atopic manifestations in a single patient, each of which responds to different underlying mechanisms, thus limiting the clinical utility of IgE testing for directing dietary interventions in patients with EoE. Indeed, because positive results from SPTs, serum IgE, and ATPs cannot be used alone to identify food triggers in EoE, food restrictions should not be recommended exclusively based on a positive result. Currently, food triggers can only be identified by documenting disease remission after specific food antigen avoidance, followed by EoE recrudescence upon reintroduction of the food in question [1]. This is the strategy used in the empirical elimination diets and food reintroduction protocols discussed below.

Empirical elimination diets in EoE

- In an attempt to overcome the disadvantages of elemental and allergytesting directed diets in children with EoE, Kagalwalla et al. explored the alternative of eliminating the six foods containing those intact food proteins most commonly associated with food allergy in children [45••]. The original 6-food elimination diet (SFED), which specifically excluded milk protein, soy, egg, wheat, peanut/tree nuts, and seafood from the subjects' diets, led to significant improvement of both esophageal inflammation (<10 eos/hpf) and symptoms in 74 % of the 35 children treated during a 6week period.
- Comparable response rates to those reported in children [46••] have also been documented for SFED in two prospective American and European series of adult EoE patients [57••, 58••] (4, grade C). It should be noted that the original list of foods restricted by Kagalwalla was broadened to include foods that gave a positive SPT result [46••, 59••], taking into account geographical food sensitization patterns [58••].
- Most importantly, using sequential single food reintroduction, researchers were able to clearly identify individual food triggers in children [59••] and adults [57••, 58••] by documenting disease recurrence through repeated endoscopies with biopsies. Cow's milk, wheat, and eggs (in that order) have been identified as the major food triggers in all available studies to date. The frequency and involvement of the remaining triggers varies from one region to another, giving rise to the question of whether empirical exclusion diets should be tailored to each specific region and based on the staple diets and food-sensitization

profiles of where the patient is being treated [58••].

- The sustained efficacy of food trigger avoidance has only been assessed in two studies [58••, 60]. For a period of up to 3 years, every patient who followed the diet remained asymptomatic, with no pathological eosinophilic inflammation seen in annual endoscopic examinations. Moreover, no drug treatment was necessary for patients with sustained remission of EoE [58••].
- Finally, allergy tests based on demonstrating an IgE-driven hypersensitivity showed limited usefulness in identifying EoE triggers in SFED-based studies, exhibiting extremely low concordance with the results of food-reintroduction challenges [57••, 58••, 59••].

Empirical elimination of cow's milk

- Cow's milk protein has been demonstrated to be the food antigen most frequently linked to EoE in both pediatric [46••, 50•, 59••] and adult patients, [57••, 58••] identified as an EoE trigger in approximately three out of four subjects.
- There are an increasing number of reports of patients developing EoE after milk [61] and egg [62] oral immunotherapy. Data on long-term food tolerance induction are still scarce [63]; the possibility of a change in the pattern of the immune response from Th2 to Th1-type should be taken into account.
- As a result, a recent retrospective study [64•] focusing solely on cow's milk showed significant histological remission of EoE (<15 eos/hpf) in 65 % of children and symptom improvement in all patients after the elimination of milk from the diet. The unexpectedly high efficacy of this strategy may have been influenced in this study by the inclusion of patients with a particular allergic background, i.e., a previous IgE-mediated cow's milk allergy undergoing desensitization.
- In conclusion, EoE patients with a previous history of Th2-mediated food allergy and who are undergoing oral desensitization should be considered for specific single-food removal, followed by endoscopic and bioptic monitoring for EoE remission. The advantages and drawbacks of re-exposing the patient to allergic reaction, including anaphylaxis in the case of accidental consumption, should be carefully weighed.

Food reintroduction and identification of food triggers

• Food reintroduction is essential in the dietary management of EoE and should always be considered after patients on elemental or elimination diets present normal esophageal biopsies. Food reintroduction has the double aim of selectively identifying foods that trigger EoE, as well as improving patient acceptance of and adherence to a less restrictive diet.

- It is worth noting that one or more independent foods can be responsible for EoE; thus, while three out of four Northwestern American (pediatric and adult) patients exhibited a single food trigger [57••, 59••], this was documented in only one out of three adult Spanish patients [58••]. Although very limited information is available on this topic, following a more varied diet (the Mediterranean diet as compared to the Northwestern American diet or an adult's diet compared to a child's), may increase the probability of developing a food allergy manifested as EoE.
- There are two possible strategies for planning the reintroduction sequence. The first is to begin with foods unlikely to cause EoE (e.g., vegetables and fruits, chicken and beef), in order to normalize the patient's diet as soon as possible [65]. The alternative strategy, assessed in SFED-based trials, consists of first reintroducing wheat and milk, because although they are the most common EoE triggers, if the result is negative, their impact in returning patients to a normal diet is higher [58••].
- After demonstrating EoE triggered by cow's milk, the immediate reintroduction of soy may provide patents with an effective milk-substitute. Due to the common cross-reactivity with cow's milk proteins, sheep's and goat's milk-derived products (mainly cheeses) should also be excluded.

How can we succeed in the dietary management of EoE patients?

- The lack of multicenter, randomized, comparative studies on the effectiveness, advantages and drawbacks of empirical elimination diets vs. skin allergy testing prevent us from undoubtedly recommending one dietary option over another. However, available evidences show that SFED seems to be the best current dietary approach for treating EoE patients, having provided the greater and more consistent results in different studies, and it should be considered for both children and motivated adults. Until better and more accurate food allergy testing capable of identifying specific food triggers is available or until genetic profiling can accurately predict individual responses to diet, the unreliability of skin allergy testing limits the use of this method to experienced centers where it has been proven to be efficient.
- Food triggers of EoE have repeatedly been demonstrated to be foods commonly consumed in the standard Western diet, including milk, wheat, and eggs. This begs the question of whether these trigger foods are the same for other geographical regions, for example, Asia, where rice and soy are common in the staple diet. Consequently, when planning a dietary intervention to manage EoE, it should be taken into account that allergy sensitization patterns depend on antigen exposure, which varies from one place to another [66–68].

- As a result, it seems reasonable to design food interventions based on skin allergy testing or empirical elimination according to the staple diet, adapting each strategy to regional consumption habits and allergy sensitization patterns.
- To date, there is no definitive data on the specific predictors of clinical response to dietary intervention in adult EoE; indeed, neither symptoms nor endoscopic/histopathological background have differed significantly among responders and non-responders [58●]. Moreover, extended experience in managing adult EoE with an SFED was associated with increased response rates (*p*<0.05) [57●]. In the case of exclusive elimination of cow's milk, younger patients and those with a lower peak eosinophil count exhibited a significantly increased remission rate [64●].
- The risk of nutritional deficiencies derived from extensive food restrictions must be adverted, especially in pediatric EoE patients. The collaboration of a dietician is strongly recommended for patient and parent dietary counseling, as a specialist can provide useful instructions and guidelines to ensure correct dietary management of the disease. The possibly harmful effects of food restrictions on adult patients seem to be minimal. In any case, extended food restrictions like those imposed in empirical SFEDs should only be used to induce disease remission over the course of several weeks. After that, food reintroduction constitutes an essential part of the dietary management of EoE patients, and should be always considered after normal esophageal biopsies have been achieved.
- Long-term difficulties in adhering to an elimination diet mostly depend on the type and number of food triggers involved in EoE. Key factors for improving adherence include finding appropriate substitutes for the eliminated foods and simplifying the food elimination study protocols. Cow's milk-based, extensively hydrolyzed formulas have been demonstrated to be well-tolerated by most adult patients with milk-triggered EoE [69•]. Ongoing research on 4-food elimination diets may simplify study protocols and reduce the number of endoscopies needed.
- Since repeated endoscopies and biopsies are essential for identifying EoE food triggers, sedation should be guaranteed for these patients, especially since it increases their willingness to undergo repeated procedures. In order to reduce the number of endoscopic exams needed, some authors have performed them after the reintroduction of two foods, but this strategy may lead to potential confusion, since symptoms do not universally reappear quickly in every patient.

Unsolved aspects & suggestions for further research

• It is interesting to note that the various dietary interventions available for EoE patients show relatively similar results with regard to efficacy, ranging from 96 to 70 % [13, 32, 44, 45••, 46••, 50•, 57••, 58••]. We can thus safely assert that in most of patients with EoE, the disease is triggered and maintained exclusively by food, with a very small remainder attributable to airborne allergens.

- Differences in the efficacy of exclusive feeding with an elemental diet compared with empirical elimination diets can be explained by allergy to those foods that are not restricted from the diet, mostly fruits and vegetables. In fact, most adult EoE patients exhibit sensitization to cross-reactive panallergen components, including profilins [70] and lipid transfer proteins (LPT), which are mostly found in food of vegetal origin.
- Because EoE is a chronic malady, foods identified as triggers for the disease should be avoided indefinitely [1]; after that, and even when a sustained drug-free response is achievable for most patients with EoE, it is tempting to speculate on the possibility of inducing food tolerance by progressive EoE trigger reintroduction. Unfortunately, the only available study on this topic provided disappointing results [59••], with EoE universally reappearing after food reintroduction in every child who had been in remission for a period of up to 4 years.
- The search for noninvasive markers of active esophageal inflammation must go on in order to facilitate the use of dietary therapies for EoE. Unfortunately, subrogate biochemical markers, including serum levels of eosinophil-derived granular proteins, have shown little usefulness in monitoring disease activity [71]. However, a novel, minimally invasive string test was recently found to accurately reflect mucosal eosinophilic inflammation by measuring eosinophil-derived proteins in luminal secretions [72]. Further research is needed to demonstrate the usefulness of this test in clinical practice.
- Finally, in order to better define novel and targeted dietary-based therapies, the many unresolved aspects concerning the immuno-logical and physiopathological mechanisms of EoE must be elucidated.

Compliance with Ethics Guidelines

Conflict of Interest

Alfredo J Lucendo and Ángel Arias declare that they have no conflicts 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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