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REVIEW
EOSINOPHILIC ESOPHAGITIS:
FROM PATHOPHYSIOLOGY TO MANAGEMENT

Nutritional approach to eosinophilic esophagitis: which diet and when

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ABSTRACT

Dietary elimination therapy has been for a long time an option for patients with eosinophilic esophagitis (EoE) and remains the only therapy targeting the cause of the disease. Different dietary approaches have been described along the last 3 decades, and cumulative evidence has defined the effectiveness and usefulness of each approach. Elemental diets are highly effective to induce EoE remission, but unpractical in most patients. Allergy testing-directed food restrictions resulted inefficient to induce remission in a significant proportion of patients (especially adults) and show a low concordance with the dietary causes of EoE. Empiric elimination diets are currently considered the most effective drug-free treatment for patients of all ages with EoE, after widely providing reproducible results. Highly restrictive empiric six-food elimination diets have paved the way to most efficient and less restrictive step-up approaches, which now include four-food and two-food elimination diets. The potential role of milk-elimination, especially in children, should be also considered. Multiple factors including demographics, nutritional status, patient and family lifestyles, social and financial support, and acceptance of repeated endoscopies influence the results of dietary therapy. Dietary therapy in EoE should be patient centered, and the patients and/or their families together with the medical provider should participate in the decision to set up this treatment. This article updates recent knowledge on dietary therapy for EoE and provides guideline to choose the most suitable alternative for patients with EoE, as well as practical tips to achieve the best results in clinical practice.

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Eosinophilic esophagitis (EoE) is a chronic, immune-mediated inflammatory disease that is characterized by esophageal dysfunction and transmural infiltration of the esophagus by eosinophils.^{1, 2} The diagnosis of EoE is reached after performing an endoscopy with biopsies in patients with a range of signs and symptoms, the most common being dysphagia and food impaction. In most cases, the natural course of the EoE is chronic and appears to be progressive, with

long-standing eosinophilic inflammation leading to esophageal remodeling with stricture formation and functional damage in the long term.³⁻⁵ Disease duration,⁶ the severity of endoscopic features⁷ and the severity of symptoms^{8, 9} significantly impair health-related quality of life (HRQoL) in patients with EoE. Because a significant morbidity may be associated to EoE, there is a need to treat patients with active disease. Treatment cessation usually leads to clinical and histopatholog-

ic relapse, thus requiring from maintenance treatment.⁷ First-line anti-inflammatory treatment options for EoE include dietary therapy, swallowed topic corticosteroids (STC) and proton pump inhibitors (PPIs).¹ As EoE represent a particular form of food allergy, diet remains the only therapy targeting the cause of the disease.^{10, 11} However, the high levels of restriction some modalities impose and the dependence on repeated endoscopies to identify food triggers have been deterrents for its generalization in clinical practice, in favor of drug-based therapies. Among drugs, PPIs is the most prescribed first-line therapy for EoE^{12, 13} despite they induce remission in only half of patients.^{12, 13} STC, including budesonide and fluticasone, have demonstrated to improve symptoms and inflammation in most of patients with EoE,¹⁴ with specific formulations designed to coat the esophageal surface inducing^{15, 16} and maintaining high rates of histological remission in the long term.¹⁷ However, dietary therapy remains as the only option that targets the primary cause of EoE and constitutes an effective and feasible drug-free alternative for many patients. This article updates recent knowledge on dietary therapy for EoE and provides guideline to choose the most suitable alternatives for patients with EoE, and practical tips to achieve the best results in clinical practice.

Rational and challenges of dietary therapy for EoE

EoE was recognized as a particular form of food allergy from the earliest descriptions of the disease. When esophageal eosinophilia was still considered a consequence of exposure to acid gastroesophageal reflux, the role of food allergy in esophageal eosinophilia was revealed: In 1995, eight out of 10 children with persistent dense esophageal eosinophilia which was refractory to antacids, antisecretory drugs and fundoplication, completely resolved symptoms and inflammation, with the other two exhibiting a significant improvement, after being exclusively fed with an amino acid-based formula (elemental diet) for 2 months.¹⁰ This seminal research established food proteins as the cause of the inflammation in EoE and clearly established that the esophagus behaves as an immunologically active organ, ca-

pable of developing allergic inflammation due to loss of tolerance to harmless antigens.¹⁸ In addition, diet was established for the first time as an effective treatment to manage EoE before other drug-based treatment alternatives were proposed. Subsequent studies confirmed the allergic nature of EoE, which is caused by a non-IgE-mediated delayed T-helper Type 2 (Th2) response to food antigens,¹⁹ with an increasingly less recognized function for environmental allergens that is not supported by most of the current evidence.²⁰⁻²² Th2 cytokines including IL-4, IL-5 and IL-13 are upregulated in the EoE esophageal tissue, contributing to eosinophilic recruitment, survival and activation in the epithelium of patients with EoE.^{23, 24} EoE usually presents in patients who associated other atopic manifestations. In fact, atopy has been linked to EoE since the initial reports of the disease, with most patients having a personal and family history of bronchial asthma or allergic rhinitis; atopic dermatitis; hypersensitivity to drugs, blood eosinophilia; or elevated serum total and specific IgE levels.²⁵ Overall, atopic manifestations are 3 to 5 times more frequent among patients with EoE compared with control subjects,²⁶ and retrospective cohort analyses in children have suggested that EoE could be a late manifestation of the allergic march, with a peak of incidence which appears after that of atopic dermatitis, IgE-mediated food allergy and bronchial asthma. A cumulative effect of multiple preceding allergic conditions in the rate of subsequent EoE diagnosis has been shown, which was higher in individuals with more than one preceding allergic condition, being IgE-mediated food allergy that with the strongest association.²⁷ Dietary therapy is effective in a significant proportion of patients to achieve and maintain long-term remission of EoE, with no need to additional chronic medication thus avoiding its potential adverse events. However, it must be considered that dietary therapy for EoE is not a panacea, and despite full adherence, a proportion of patients will never respond. Dietary therapy requires large motivation and effort by the patient and family, organization skills, time for shopping or to cook, and abilities to cope with social settings.²⁸ However, this will not guarantee success. The decision to set up a dietary treatment must be shared and

agreed by the patients and/or their parents, who in the case of children 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.^{29, 30} Among responders, 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

Choosing right patients for dietary treatment: the first key to success

Multiple factors must be considered before opting for an elimination diet, largely individualized to each patient’s situation. Best candidates for dietary therapy 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. The moment to start a diet should be arranged, trying to avoid vacation periods or planned trips during the months the patients is on the diet. Social events that revolve around food, should be restricted during the study period with an empiric elimination diet. Some patients should be discouraged for dietary therapy, as those suffering from IgE-mediated food allergies, which are common comorbid conditions in children with EoE, or those who are subjected to additional food restrictions, as gluten-free diet for patients with celiac disease.³¹ Food patients usually avoid will not cause EoE, so additional restrictions should be added to the former, thus impairing HRQoL and hindering social activities. In addition, patients suffering malnutrition, feeding difficulties and those with self-restrictive behaviors toward food are not best candidates for dietary therapy, and should be considered to be better managed with PPIs or STC. On the other hand, patient lifestyle and their family habits should also be considered when projecting dietary therapy; the initial phases of an elimination diet are usually the most restrictive and make it virtually impossible to eat at restaurants or consuming highly processed products. The time needed to buy food stuffs and cooking them at home should be considered, as well as patients’ work and school schedules. A proper adherence

to the diet will require to have lunch at home or take his/her prepared food to work or school. Parents, caregivers or family members responsible for providing food to patients must be informed and have the skills to support the patient’s diet.³² The cost of food-elimination therapy should be also considered, as they entail additional expenses for patients with EoE or their families. They must be informed they will need to buy unprocessed foods in grocery shops instead of supermarkets due to difficulties in finding processed foods free of milk, gluten, eggs, or soy, of if food allergen labeling is not complete. A study in the United States estimated that a six-food elimination diet (SFED) resulted in a 17.4% weekly cost increase regarding a regular diet.²⁹

Facility-related aspects required for treating EoE patients with diets

Not only aspects related to the patient, but also to the healthcare center, should be considered when offering the possibility of dietary treatment to patients with EoE: The effectiveness of every elimination diet should be evaluated with an endoscopy with biopsies, generally performed after a period of 6 to 8 weeks, which has been considered the minimum length of time to achieve histologic remission of EoE (Figure 1). Only a minority of authors have prolonged food restriction before endoscopy up to 12 weeks.^{33, 34} Once histologic remission of EoE is achieved, patients should be advised to consume or be exposed to a certain amount of each reintroduced food almost

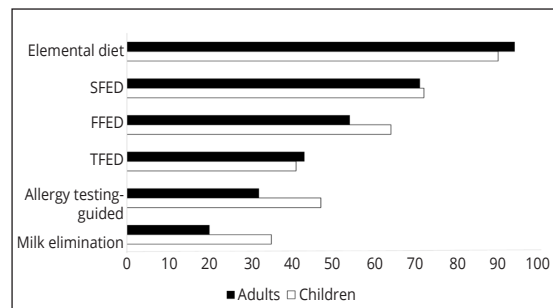


Figure 1.—Histologic remission rates broken down by age group and shown by different modalities of dietary therapy (elemental diet, empiric elimination diets, and allergy testing-guided elimination diet) for EoE. SFED: six-food elimination diet; FFED: four food elimination diet; TFED: two-food elimination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

daily, with an endoscopic procedure after each individual food reintroduction. The site must be able to schedule endoscopies in an agile way, usually after periods of 6 weeks, and to be able to reschedule them even to shorter periods of time in case patients present symptoms. Any case, 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,^{35, 36} conditioned to the lack of recurrence of inflammation in the immediately preceding endoscopy. In addition, providing 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.³⁷⁻³⁹ Repeated propofol sedation is considered safe, even in children.⁴⁰ The participation of a dietitian to support patients with EoE undergoing dietary therapy have been matter of controversy. 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.³⁰ A dietitian can certainly be of enormous benefit for some patients, but important research on dietary therapy, especially in adults, have also achieved excellent results with no involvement of this professional.⁴¹⁻⁴³ The participation of a dietitian takes more importance in the case of small children, because up to one third of them may present evidence of failure to thrive, likely secondary to malnutrition⁴⁴ caused by feeding dysfunction.⁴⁵ A detailed assessment of their diet pretherapy, their nutritional status and presence of any feeding difficulties is needed in this scenario in order to know whether a diet will be feasible.²⁸ Any case, growth failure and feeding difficulties are not a contraindication for a dietary elimination therapy, as this, if effective, will be resolved both even in the short term.⁴⁶ Nutrition assessment in these poorly nourished patients should involve

additional nutritional planning for provision of adequate calories for catch up growth, and appropriately replacing or supplementing removed foods.³²

Elimination diet option: which diet should we use?

Once it has been agreed that a patient with EoE is a good candidate to be treated with a food elimination diet, the next aspect is to choose the best dietary option to be offered. When choosing a diet treatment option, we should consider not only the comparative efficacy of each of them, but also the practical and clinical aspects that may determine effectiveness and adherence in the longer term.

Elemental diet: a mere bridge therapy towards other options

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 being first implemented by Kelly *et al.* in 1995,¹⁰ subsequent studies further corroborated that elemental diet rapidly induced remission of symptoms and esophageal inflammation in most patients, with a meta-analysis summarizing the effectiveness of elemental diet to induce histologic remission of EoE in 90.9% of patients,⁴⁷ with improvement of symptoms and endoscopic finding of the disease in most cases. Most of studies on elemental diet have been carried out in children⁴⁸⁻⁵² and have revealed that many patients may not accept the flavor of the amino acid-based formula despite the current availability of a variety of flavors, therefore requiring tube feeding in a high proportion of cases.⁵⁰ More recently, two prospective studies have also evaluated the effectiveness of elemental diets in adults. Adherence to the diet represented a problem and abandonment of the protocol was common. Any case, the high effectiveness of the diet was comparable to that reported for children among the adult EoE patients who avoided any kind of food except an elemental formula for a 4-week period.^{53, 54} Recently, a modified elemental diet that allows 1-2 foods of low allergenic potential to be concurrently consumed with the amino acid-based formula, have been proposed

so that not to delay oral sensory and motor developmental milestones, which are crucial in infants and toddlers and are likely to be already delayed in these patients due to early onset EoE with associated difficulty and/or pain swallowing.^{32, 55} In fact, in children under 2 years-old with known feeding dysfunction, long term avoidance of solid food may lead to delayed oral-motor skill development.⁵⁶ The potential advantages of this modified elemental diet have not been, however, evaluated in clinical practice. Despite its high effectiveness, comparable to most recently developed pharmacological therapies for EoE,¹⁶⁻⁵⁷ elemental diet seems unfeasible in clinical practice for a variety of reasons. Aside of its poor palatability and need of nasogastric tube feeding in a proportion of children to ensure a proper intake of calories and potential risk for delayed oral motor skill development, elemental diets negatively impact over social activities and psychosocial well-being, which are essential components of HRQoL in patients with EoE.⁵⁸ The high cost of elemental diets is not universally reimbursed by insurances and represents an additional barrier for implementing elemental diets, further restricting the potential utility of this therapy in patients of EoE. It has been proposed that elemental diet may have a role in refractory patients who wish to remain in remission while investigating the casual role of unusual foods and aeroallergens in their disease⁵⁹ (for which to sequentially re-introduce foods with follow-ups via upper endoscopy with biopsies will need many visits to the clinic, excessive costs and procedure-associated risks), or as a bridge therapy while waiting for investigational drugs.¹ However, these potential utilities, have not been assessed yet.

The failure of allergy-tests directed food elimination diets

The demonstration of EoE as a particular form of food allergy and the unfeasibility of elemental diets for many patients led to allergist to try to identify food triggers by food allergy testing, in order to achieve disease remission after a diet tailored for each patient. After the definition of EoE as delayed Th2-mediated disease¹⁹ and the demonstrated utility of skin testing in identifying food triggers, particularly milk, in atopic dermatitis,⁶⁰ a Th2-mediated allergic disease similar to

EoE, allergists took the initiative of dietary treatment of EoE. In a large series of children with EoE Spergel *et al.* avoided the foods that test positive in both skin prick tests (SPT) and atopy patch tests (APT), aimed to eliminate immediate IgE-mediated and delayed T-cell mediated reactions to foods (at that moment EoE was considered as a mixed disturbance).^{61, 62} The effectiveness to induce histologic remission provided by this strategy, and after eliminating an average of 5 foods from each children's diet, ranged between 49%-53%. A meta-analysis that summarized these studies together with subsequent reports on the effectiveness of allergy testing food-elimination in EoE (including all combinations of SPT, APT and serum-specific IgE to food) revealed that allergy testing-based elimination diet led to histologic remission in 45.5% of patients, with wide heterogeneity (with a heterogeneity I² of 75%) indicating a low reproducibility.⁴⁷ Of note, its effectiveness was significantly lower in adults than in children (32.2 *versus* 47.9%) (48). Data in children have come mostly from a single center, and numerous pediatric studies have not replicated that center's efficacy rates using SPT or APT. Results in adults were consistently disappointing.^{35, 36, 63} As a result, guidelines and consensus documents do not recommend this strategy to guide dietary interventions in patients with EoE.^{1, 64} One of the biggest criticism to the early studies by Spergel *et al.* is that, after achieving EoE remission, food triggers were not identified by documenting histologic recurrence of eosinophilic inflammation in esophageal biopsies, but rather by symptom relapse reported by parents after individual food reintroduction. Of note, a low correlation between symptoms and histological activity in EoE has been repeatedly demonstrated.⁶⁵⁻⁶⁷ The sensitivity and specificity of allergy tests to identify food triggers for EoE has been demonstrated consistently low; 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 is insufficient to guide clinical practice: In children, 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%).⁶⁸ Likewise, results

for APT followed a similar trend, with PPV ranging from 12% to 86.2% (average 44%), and low NPV for milk (40%), egg (56%), and wheat (67%) among children with EoE.⁴⁹ The combination of SPT and APT yielded a poor average PPV (44%) but allowed to increase the average NPV (92%), except for milk, which continued to show a low NPV (44%).⁶² In adults with EoE, the predictive ability of alternative allergy testing to SPT and APT to identify foods responsible for the disease was further investigated.³⁶ Food triggers for EoE were identified in a prospective series of 20/23 adult patients who responded to an empiric SFED and underwent to subsequent food challenge. Five allergy testing modalities were performed at baseline 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. Therefore, food allergy tests should not be used to guide the dietary management of EoE, since the results of these tests are not sufficiently precise to consider or exclude any food as a potential cause of EoE. Therefore, its use in the clinic should be abandoned, in favor of dietary treatment strategies with reproducible efficacy.

Empiric elimination diets: a reproducible but still imperfect strategy

Empiric elimination diets were, chronologically speaking, the last type of dietary strategy used to treat patients with EoE in clinical practice. Different modalities of empiric elimination diets are currently the most commonly used dietary approaches for treating EoE and consists of avoidance of common food allergens without any allergy testing. The development of this kind of therapy was based on the concept that avoidance of foods that commonly cause immediate food hypersensitivity could also resolve EoE and appeared in response to the very restrictive nature of elemental diets and the poor and inconsistent results of allergy test-directed food elimination.

In the first retrospective study on this approach by Kagalwalla *et al.*,⁵¹ a group of children with EoE were advice to restrict from their diets milk, wheat, egg, soy, peanuts/tree nuts and fish for a 6-week period. After this six-food elimination diet (SFED), histological disease remission was achieved in 74% of the patients treated. Subsequent studies, including prospective ones and carried out in both children and adults, reproduced similar rates of effectiveness.^{41, 69} A meta-analysis of seven observational studies assessing SFED in patients of all ages provided an extremely homogeneous (I^2 statistic = 0) histologic remission rate of around 72% (95% CI, 66-78%),⁴⁷ revealing it as the most reproducible dietary approach for EoE. In patients who achieve remission, sequential food reintroduction under endoscopic and biptic control allows the identification of individual food triggers for each patient, by documenting disease recurrence after exposure to food. Maintenance of remission in the long term should be done by exclusively avoiding the food or foods with demonstrated capacity to trigger EoE.⁷⁰ 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,^{41, 71} making it feasible the adherence to the diet in the long term. Small variations in the exact foods removed in the different studies dealing this empiric SFED have been shown,²⁸ including removing shellfish additionally to fish, all legumes instead of soy and all grains including rice, corn, and all gluten-containing cereals instead of wheat. The clinical relevance of these small differences seems negligible, and in essence they do not affect the meaning of an empirical elimination diet, the basis of which is to dispense with the foods that most commonly trigger food allergies, and which may present small variations depending on food consumption habits and sensitization pattern of the different populations assessed. A handful of studies have assessed the effectiveness of this diet in the long term: In children followed during a period of 1-2 years, no treatment-related complications, nutrient deficiencies or growth deceleration were noted.⁷¹ However, EoE relapsed in all cases on rechallenge with known food triggers. In adults, those who strictly avoided foods known to trigger EoE maintained symptoms

controlled and histological remission for up to 3 years, together with reversion of endoscopic features of EoE.^{41, 69, 72, 73} However, a high rate of non-adherence and diet cessation were reported in the most recent studies, which limits the number of patients remaining on a food elimination diet in the long term. The high level of restriction imposed by removing six food groups from patients' diet and the fact that most of responding patients will have only one or two food triggers for EoE, being milk, wheat/gluten, egg and soy/legume those most commonly involved, promoted new attempts at reducing the number of empirically avoided foods. Two prospective, multicenter trials, conducted in children⁴⁶ and adults,⁴² used empiric four-food elimination diets (FFED), consisting of avoidance of milk, gluten/wheat, egg and soy/legumes provided clinicopathological remission rates of 64% and 54%, respectively.

Step up empiric elimination diets: reversing the approach

A FFED reduced the level of restriction and the number of endoscopies compared to a SFED, allowing the consumption fish/seafood, peanuts, and tree nuts in the diet with despite slightly reducing effectiveness. However, 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.³⁰ Molina-Infante *et al.* tested for the first time a step-up empiric dietary approach in a multi-center study involving 130 children and adults with EoE who underwent a TFED.⁴³ Non-responders to the TFED were then offered a FFED, and non-responders to FFED were offered the SFED. A TFED achieved both histologic and symptomatic remission of EoE in 43% of patients. In non-responders to a TFED, stepping up to an FFED (60%) and a SFED (79%) led to remission rates similar to those previously reported. Importantly, no differences between pediatric and adult patients were found. Compared with a top-down strategy, this step-up approach reduced the number of endoscopic procedures and shortened

the diagnostic process time by 20%, while avoiding unnecessary dietary restrictions (43% of study patients could find their triggering foods without eliminating egg, legumes, nuts and fish/seafood, and up to 60% while consuming nuts and fish/seafood). Additionally, 90% of responders to a TFED or FFED were found to have just one or two causative food groups, thus identifying responders with few food triggers relatively rapidly. This study also showed that 90% of responders to a SFED with previous failure to a TFED and FFED were found to have three or more food triggers, making it difficult to maintain a proper adherence to the diet in the long term. Consequently, a SFED might be discouraged within the step-up strategy, or merely reserved for exceptionally motivated patients who still want to elucidate their food triggers, even though they might be numerous. A retrospective study based on a European registry of children with EoE recruited at 13 countries have recently confirmed results on the effectiveness of a step-up approach: The efficacy rates were 68% for a SFED, 46% for a three-food elimination diet (milk, wheat, and egg) and 32% for a TFED.⁷⁴ Recently, a step-up empirical food elimination has been demonstrated the most efficient dietary approach for patients with EoE according to a computer-based simulation model which compared different strategies for dietary therapy in EoE:⁷⁵ The potential effect of eliminating up to 12 foods known to induce EoE, balanced by the number of endoscopies required to complete the food reintroduction strategy and identifying culprit foods were assessed. 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. The predicted ability of this model should be further evaluated in clinical studies.

Milk elimination diet: what is the next step?

All studies based on empiric food elimination have identified milk as the most common food in triggering and maintaining EoE in patients of all ages. Therefore, a cow's milk elimination diet has been proposed as simpler dietary approach and the easier way to check the effectiveness of

a dietary intervention in EoE. Some evidences on the effectiveness of avoiding milk from children's diets have been provided in the literature, with histologic remission rates reported to range around 60%.^{52, 76} However, methodological issues flawed these studies, overestimated the effectiveness of this dietary intervention by including patients with EoE induced after oral milk desensitization to treat IgE-mediated cow's milk allergy⁵² and other who concomitantly used PPIs during cow's milk elimination,^{76, 77} a drug able to achieve clinical and histological remission in 50% of patients with EoE.⁷⁸ Recently, better designed retrospective studies provided effectiveness rates ranging from 25% to 58%.^{33, 74, 79} 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). Prospective studies specifically designed to assess the efficacy of milk diet in children and adults are warranted. Finally, 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.⁷⁵

Implementing dietary therapy in clinical practice: further keys to succeed

As previously said, the decision to set up a dietary treatment must be shared and agreed by the patients and/or their parents. Dietary therapy must be patient-centered and before initiating it, potential short and long-term barriers for its implementation should be identified. Patient and family lifestyles and habits should also be considered; the most restrictive phases of an elimination diet make it virtually impossible to eat at restaurants or consuming highly processed products, so time to buy food stuffs and cooking them at home should be available. Social events that revolve around food should be avoided. 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. Patients must receive detailed information on expected re-

mission rates obtained with each dietary option, and 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. All elimination diets should be instituted for a minimum of 6 weeks and always followed by endoscopic assessment with compulsory esophageal biopsies. Symptomatic improvement alone of a lack of endoscopic findings of EoE are not accurate enough to inform on histologic remission of EoE and are insufficient to guide de reintroduction process.⁸⁰ Once histologic remission of EoE 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. As said before, a recent study suggested that 2 weeks may be sufficient to induce the histopathological changes that define active EoE after food challenge.³⁵ The more food removed, the longer the food reintroduction process will take, therefore intermittent breaks during the process are allowed. 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. They should be instructed also 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 hydrolysates, however, are well tolerated by EoE patients.⁸¹ As for wheat, risk of cross-contamination and concerns of possible cross-reactivity among related grains of barley and rye⁸² would need to restrict gluten from patients' diets.

Conclusions

In conclusion, dietary therapy is the only treatment that targets the primary cause of EoE and

not the inflammatory consequences of the disease, therefore it constitutes a first line therapy for this disease in a proportion of patients. Selecting good candidates constitutes a key aspect for success. Empiric elimination diets have demonstrated the best effectiveness/reproducibility ratio and are the only approach to be currently recommended to patients. Despite a SFED has been key to identify the causative foods that trigger EoE, the high level of restriction and large number of endoscopies that this modality requires have displaced it towards simpler and less restrictive options. Among them, step-up empiric elimination diets currently represent the initial dietary approach for EoE in most patients. However, evidence suggest that a milk elimination diet could be considered in children with EoE.

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