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Food elimination diets in eosinophilic esophagitis: Practical tips in current management and future directions

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ABSTRACT

Eosinophilic esophagitis (EoE) is a chronic, antigen-mediated disease of the esophagus characterized by symptoms of esophageal dysfunction and an eosinophil-predominant inflammation. Seminal reports identified the role of food allergens in the pathogenesis of the disease by demonstrating that food avoidance could lead to the resolution of esophageal eosinophilia in EoE patients. Although pharmacological treatments for EoE are increasingly being investigated, the exclusion of trigger foods from the diet still represents a valuable option for patients to achieve and maintain disease remission without drugs. Food elimination diets are variegated, and one size does not fit all. Accordingly, before starting any elimination diet, patients' characteristics should be thoroughly evaluated, and a rigorous management plan should be defined. This review provides practical tips and considerations to succeed in the management of EoE patients undergoing food elimination diets, as well as recent advances and future perspectives on food avoidance strategies.

Research agenda

- The role of combined dietary and pharmacological therapies, and potential benefits compared to monotherapies should be investigated further
- The contribution of inhaled and subsequently swallowed allergens in EoE should be elucidated
- Long-term follow-up studies on the efficacy of and compliance to diet are necessary
- Further data on the performance and viability of non-endoscopic monitoring strategies are required

Practice points

- A rigorous management plan should be defined before starting an elimination diet
- The involvement of a dietitian is recommended to provide practical guidance to patients and families
- Food elimination diets should be tailored on patients' characteristics and preferences
- A step-up, as opposed to a top-down, food elimination diet is effective and practically more viable in clinical practice

1. Introduction

Eosinophilic esophagitis (EoE) is a chronic, progressive, antigen-mediated disease characterized by symptoms of esophageal dysfunction and an eosinophil-predominant inflammation restricted to the esophagus [1]. Different factors have been associated with the impairment of esophageal mucosa, including genetic factors, gastro-esophageal reflux disease, and microbiota composition [2–4]. The disease is diagnosed in patients reporting esophageal symptoms when at least 15 eosinophils per high power field (eos/HPF) are found in at least one esophageal biopsy [5]. Other than eosinophils, several other immune cells, including mast cells, basophils, and lymphocytes participate in the inflammatory response to food and inhaled antigens penetrating through a defective esophageal mucosal barrier [6]. The clinical presentation varies with age: adults commonly complain of typical symptoms such as dysphagia and episodes of bolus impaction, while children usually present with non-specific upper gastrointestinal symptoms including reflux-like symptoms, nausea, vomiting, and failure

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to thrive [1]. In addition, esophageal dysmotility may contribute to symptoms in a proportion of patients [7,8]. The incidence and prevalence of the disease have been constantly increasing since its first recognition as a result of both increased awareness and a true increase of the incidence [9]. Current estimates report incidence rates of up to 20 per 100,000 people per year, similar to that of inflammatory bowel diseases (IBD) [10–12]. The current prevalence is more than 1 in 1000 people in Western Countries, and of 20 every 100,000 upper endoscopies in Asia [10].

The treatment of EoE includes pharmacological and non-pharmacological options. Proton pump inhibitors (PPI), topical steroids, and monoclonal antibodies are already available in clinical practice, and novel drugs are currently being investigated and will be available soon [13–16]. On the other hand, food elimination diets are the only drug-free alternative that effectively treats the disease and represent an appealing option for patients unwilling to take drugs long-term [17]. The following narrative review aims to provide tips on practical aspects and relevant considerations for a successful dietary management of patients with EoE. In addition, recent advances and future perspectives on food avoidance strategies will be discussed in the following paragraphs.

2. Literature search

We reviewed original research articles, reviews, and clinical trials describing dietary treatments in patients with EoE. The literature review was conducted using the electronic databases PubMed, MEDLINE, and the Cochrane Library from inception to December 2022. We included original articles, clinical trials, and systematic reviews with meta-analysis investigating or discussing the dietary management of EoE. Two authors independently reviewed all manuscripts. All trials data was included as well other literature was included, based on a consensus decision of scientific merit by the reviewing authors. Additionally, the references listed in online databases publications were manually reviewed to increase sources of information.

3. Why a drug-free treatment works in patients with eosinophilic esophagitis

When EoE was not yet recognized as a distinct clinical entity, it was believed that esophageal eosinophilia was merely a consequence of gastroesophageal reflux [18]. However, although reflux impairs esophageal mucosal barrier and may play a role in some patients [19,20], several studies have demonstrated that esophageal inflammation in EoE is precipitated and sustained predominantly by food antigens penetrating through a defective esophageal mucosal barrier [6]. In this regard, early reports and more recent studies have demonstrated the pathogenetic role of food in patients with EoE, by showing that the use of antigen-deprived feeding formulas could lead to the resolution of esophageal eosinophilia if all kind of table food was avoided [18,21,22]. These findings were further corroborated by the fact that the reintroduction of food induced the recurrence of esophageal inflammation [18,21,22]. Other studies subsequently revealed that the recurrence of esophageal eosinophilia was triggered by the reintroduction of only some specific foods [23–27], which allowed to take a step forward towards tailored dietary regimens in which only patient-specific trigger foods are avoided. Several food elimination diets are currently available, and the best choice depends on individual patients' characteristics, as well as healthcare related factors.

4. What diets are available for the treatment of EoE

Since Kelly et al. [18] demonstrated the efficacy of diets with amino acid-based formulas in children with EoE three decades ago, further studies have corroborated the therapeutic role of diet in EoE (Table 1). Elemental diets represent a highly effective dietary treatment for EoE with histologic remission rates of around 90% in both children and adults [22]. However, despite impressive remission rates, the complete avoidance of all kind of solid foods is unpractical in daily life and is poorly tolerated by patients as a long term strategy. The main reasons for this include the poor palatability, high costs, significant psychosocial deterioration, and impairment of the quality of life (QoL) that patients experience when undergoing a highly restrictive diet [28]. Accordingly, in clinical practice, elemental diets should be offered to highly selected, compliant patients who seek disease remission while investigating the causal role of unusual foods and aeroallergens for their disease [29], or as a bridge therapy while awaiting investigational drugs [13,30,31].

Table 1
Efficacy of available empiric elimination diets for inducing histologic remission in pediatric and adult patients with EoE.

	Avoided foods	Efficacy (<15 eos/hpf)		Trigger foods prevalence	
		Children	*Adults*	*Children*	*Adults*
Elemental diet	Only elemental formula allowed	90.4%	94.4%	–	–
OFED [40,47]	Cow's milk	50%	27%*	–	–
TFED [40]	Cow's milk, wheat	44%	40%	**68% one food trigger:** Milk 52% Wheat 15%	
FFED [37,82]	Cow's milk, wheat, eggs, soy/legumes	64%	54%	Milk 84% Wheat 28% Egg 8%	Milk 50% Wheat 31% Egg 22%
SFED [32,33,83]	Cow's milk, wheat, egg, soy/legumes, nuts, fish/seafood	73%%	71%	Milk 74% Wheat 26% Egg 17%	Milk 50–62% Wheat 29–60% Egg 26%

Abbreviations. OFED: one-food elimination diet; **TFED**: two-food elimination diet; **FFED**: four-food elimination diet; **SFED**: six-food elimination diet; *indirect estimates from studies on FFED/TFED.

Empiric elimination diets, consisting in the avoidance of the most common allergenic foods known to trigger EoE, subsequently emerged as the standard dietary approach in clinical practice. Empiric elimination diets are more practical and better tolerated by patients than elemental diets. The six-food elimination diet (SFED) represents the most restrictive empiric elimination regimen, and consists in the avoidance of milk/dairy, gluten/wheat, egg, soy/legumes, nuts, and fish/seafood. The SFED has consistently shown high efficacy in achieving histologic remission in both children (73%) and adults (71%) with EoE [22,32–34]. Historically, patients undergoing SFED would be asked to avoid all the six food groups to induce disease remission, followed by serial reintroduction of single food groups, with each reintroduction followed by endoscopy with histological assessment. This strategy, known as "top-down" [35], allowed to identify the specific group of foods that caused the recurrence of esophageal eosinophilia whose avoidance would maintain disease remission (Fig. 1). However, due to the high level of dietary restrictions, the time needed to complete the exclusion and reintroduction phases and the high number of endoscopies to undergo after each avoidance and reintroduction, the top-down approach is currently somewhat unpopular among patients and caregivers [36].

Subsequent studies revealed that the most common causative foods in SFED responders were cow's milk, wheat, and egg, with nuts and fish/seafood playing only a marginal role. Accordingly, up to three-quarters of responders to a SFED were found to only have one or two trigger foods [35]. These findings paved the way for the development of a simpler and easier diet, called four-food elimination diet (FFED), in which only cow's milk, wheat, eggs and soy/legumes are avoided [37]. In this regard, in a multicenter prospective non-randomized study conducted in

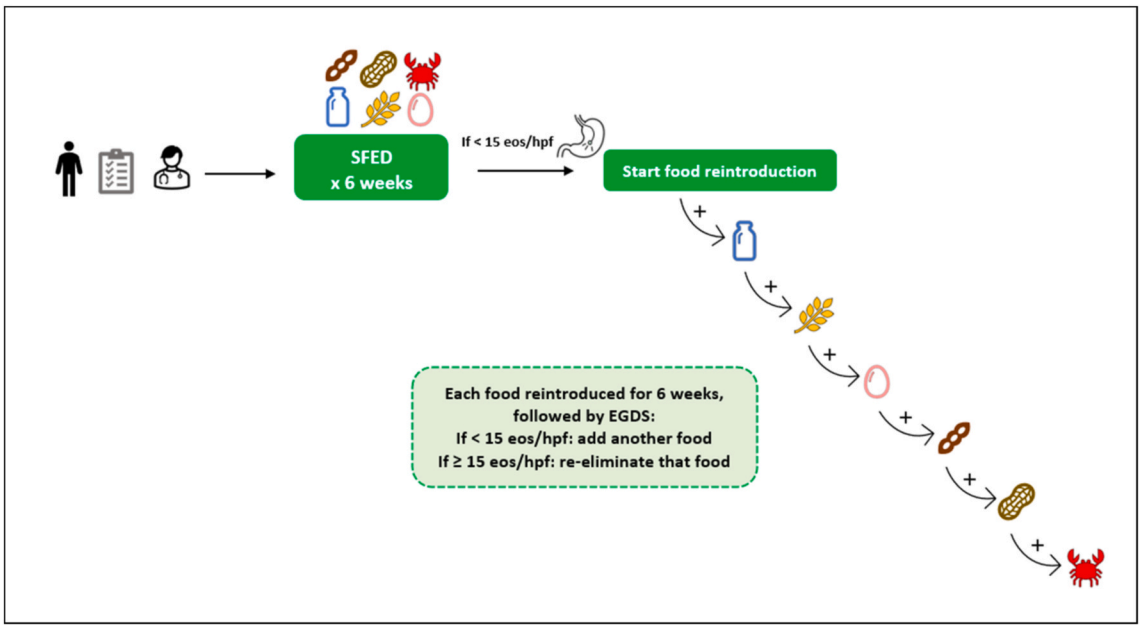

Fig. 1. Top-down strategy for the six-food elimination diet.
Abbreviations. SFED, six-food elimination diet; **eos/hpf**, eosinophils per high-power field; **EGDS**, esophagogastroduodenoscopy.

52 adults with EoE, the FFED induced histologic remission in 54% of patients. Of note, 50% and 30% of the responders to the FFED were found to only have cow's milk or wheat as trigger foods, respectively [38]. In addition, in a study conducted in children undergoing FFED, remission was achieved in 64% of cases [39]. Similar to adults, up to 55% of pediatric FFED responders had cow's milk as the only causative food identified during the serial single-food reintroduction phases. Both studies [38,39] showed that around a half of responders to a FFED could have adopted a less restrictive dietary approach to achieve histologic remission, by only withdrawing cow's milk and wheat. Accordingly, a simpler dietary scheme, the two-food elimination diet (TFED), became appealing for both clinicians and patients.

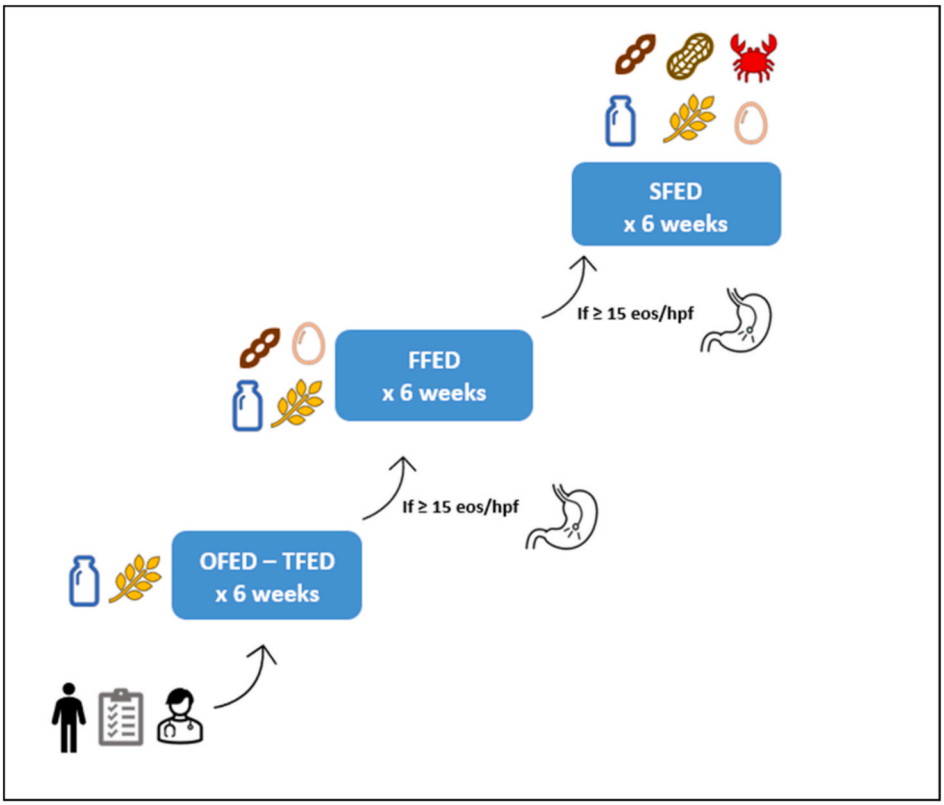

Fig. 2. Step-up strategy for the six-food elimination diet.
Abbreviations. OFED, one food elimination diet; **TFED**, two food elimination diet; **FFED**, four food elimination diet; **SFED**, six-food elimination diet; **eos/hpf**, eosinophils per high-power field.

A multicenter study validated the TFED as a viable and effective dietary approach in EoE [40], and represented a significant turning point in the setting of empiric elimination diets. The study enrolled 130 patients among children and adults with active EoE. All patients underwent TFED (cow's milk and wheat) and, after six weeks of treatment, clinical and histologic remission was achieved in 43% of patients. In those who had histologically active EoE despite the TFED, the elimination diet was escalated to a FFED and, eventually, to a SFED in case of failure to respond to the FFED. As expected, the higher degree of restriction improved the outcomes of the TFED, with 60% of patients undergoing FFED and 79% of those undergoing SFED achieving disease remission [40]. This study showed that a "step-up" strategy (Fig. 2), in which the degree of dietary restrictions increases progressively, can be effective and significantly shortens the diagnostic workup, reducing the number of endoscopies by 30% compared to the historical "top-down" approach. In addition, the study found that up to 90% of responders to the TFED or FFED only had one or two trigger foods (milk and wheat) [40]. In contrast, those who failed the TFED and the FFED, and were subsequently escalated to a SFED were more likely to have at least three causative foods, including nuts and fish/seafood. These findings suggest that the more patients with EoE need escalation of the step-up strategy, the higher is the likelihood of having multiple food triggers. In this regard, patients who respond to the avoidance of few foods are also those who are more likely to be compliant to the diet in the long term, as it becomes progressively more difficult to adhere to the diet when a high number of foods needs to be avoided [17,41]. Consistently, it has been shown that up to 70% of SFED responders may lose adherence in the long term [42]. Therefore, in clinical practice, a step-up approach, as opposed to a top-down strategy, should be preferred when proposing an empiric elimination diet. However, a top-down strategy could still be valuable for highly motivated patients who are willing to undergo the most effective, although highly restrictive, among empiric elimination diets.

Several studies have shown that cow's milk is the most common food trigger in EoE [27,35,38]. Therefore, subsequent retrospective studies have investigated the efficacy of a milk-free elimination diet, showing variable remission rates between 58% and 65% [43–45], although another retrospective study conducted on the European pediatric registry showed lower remission rates of around 25% [46]. In contrast, a recent prospective multicenter study [47] conducted in children with EoE treated with a one-food elimination diet (OFED) in which all cow's milk proteins were excluded, showed that histologic remission could be achieved in more than 50% of patients. Of note, most patients in the study were concomitantly taking a PPI, limiting the possibility to draw strong conclusions on the effectiveness of the diet.

More recent studies on IgE-mediated food allergies have demonstrated that different milk processing techniques, such as heat treatment or enzymatic hydrolysis, might prevent allergen sensitization and reduce the food immunogenicity [48]. Accordingly, although EoE is thought to be a non-IgE mediated disease [49] and despite the specific milk protein triggering EoE remains unknown, several studies have investigated the effect of processed cow's milk in patients with milk-induced EoE. In particular, a retrospective study assessed the tolerance of baked milk in 15 children in which cow's milk had been identified as a causative food. Of note, 73% of patients maintained histologic remission while being fed with baked milk [50]. In another study, EoE patients in histologic remission with proven milk-induced EoE were given 200 ml of sterilised (boiled) cow's milk twice daily for eight weeks. At week eight, 12/18 patients were still in histologic remission. In addition, clinical and histological remission were maintained for up to one year in patients who regularly consumed sterilised milk [51]. In a similar fashion, a prospective study showed that 15/17 (88%) of adult patients with proven cow's milk-induced EoE, maintained remission while being fed with fixed amounts of milk-based extensively hydrolyzed formula [52].

5. Mainstays for a successful dietary treatment: how to plan a diet

EoE is a chronic condition whose peak incidence is in young age and requires a potentially life-long treatment plan. Accordingly, elimination diets may represent an appealing drug-free alternative for some patients who are unwilling to take drugs long term. However, it should be acknowledged that the choice to undergo dietary restrictions is resource-demanding for both patients and caregivers. Specific healthcare resources should be guaranteed to suitable patients, and patient-related factors should be considered when managing patients undergoing food elimination diets (Table 2).

5.1. Healthcare resources

A good management plan is crucial to succeed in the dietary management of EoE long-term. In addition, before proposing any food elimination diet, the clinician should be confident that the diet will be clinically safe for the patient. Accordingly, a general clinical assessment, including a thorough evaluation of the nutritional status and possible feeding difficulties in children, is required to assess whether the diet is viable [53].

It is now recognized that elimination diets require the involvement of experienced dietitians during both the elimination and the reintroduction phases [54]. In this regard, a recent systematic review showed that food restrictions in EoE may be burdened by the risk of nutritional deficiencies [55]. In a recent prospective study conducted in patients with EoE or gastroesophageal reflux disease (GERD), although serum nutritional markers were normal in both groups, food diaries showed suboptimal dietary calcium and vitamin D intake in those with EoE [56]. Additionally, children with EoE seem to be at higher risk of abnormal feeding behaviours and feeding dysfunction both when the esophageal inflammation is ongoing and when the disease is in remission [56,57]. Given the complexity of food elimination diets, the involvement of an experienced dietitian is important to mitigate risks and to help patients to succeed in elimination diets. The support of a dietitian is crucial to provide personalized education and practical guidance on how to maintain a nutritionally balanced and palatable diet [58]. In addition, a multidisciplinary management of EoE may improve the success of elimination diets and is currently strongly recommended by international guidelines [54,59].

Another important aspect of the dietary management of EoE is the necessity of frequent endoscopies in the early phases of the diet [17]. For instance, when a top-down SFED is chosen, the first follow-up endoscopy is performed after the avoidance of six food groups for at least six weeks. Subsequently, SFED responders undergo a repeat endoscopy after a

Table 2
Healthcare resources and patient-related factors in the dietary management of eosinophilic esophagitis.

Healthcare resources	Patient-related factors
1 A rigorous management plan should be defined in advance and subsequently adhered to.	1 Patients and family should acknowledge the increased costs and burden for shopping.
2 A strict schedule for outpatient visits and endoscopic assessments should be guaranteed.	2 Patients' motivation and long-term adherence are a mainstay.
3 A thorough evaluation of the nutritional status and possible feeding difficulties should be assessed at baseline.	3 Patients should be prepared to the possibility of a negative impact on the quality of life.
4 The involvement of an experienced dietitian is required to provide personalized education and practical guidance on how to maintain a nutritionally balanced and palatable diet.	4 Organizational skills to prepare meals, especially when eating out of the house, are required.

minimum of six weeks after each food group reintroduction, accounting for up to 6 endoscopies in one year in those who are eventually found to have only one group of trigger foods [27]. Given the highly demanding diagnostic work-up, before embarking on elimination diets, a strict schedule for outpatient visits and endoscopic assessments should be defined on the first consultation, to reduce the number of weeks that patients spend undergoing unnecessary restrictions. In addition, the endoscopy service should be able to offer endoscopic procedures at any time during the reintroduction process in case of symptoms recurrence [41]. Accordingly, an efficient and reliable endoscopy service that can meet pre-established deadlines is crucial when undertaking an elimination diet.

5.2. Patient-related factors

Patients' motivation is another mainstay for the success of elimination diets. Patients should be made aware of the inevitable challenges that will come with the diet. In a real-life study investigating the cost and ease of shopping for patients undergoing a SFED compared to an unrestricted diet, it was shown that adherence to the SFED cost on average $660 a year more than an unrestricted diet, and required a higher proportion of items purchased at a second store [60]. Accordingly, both patients and families should be informed that an elimination diet will probably increase shopping costs and the logistical burden for the shopping.

EoE invariably relapses following treatment discontinuation [1]. Therefore, once remission is achieved, dietary restrictions should be consistent over time to maintain the benefits. In this regard, although diet is effective in the short-term [61,62], it has been shown that loss of response due to nonadherence to diet is common in the long-term [63]. A three year follow up study on patients who identified offending foods following SFED and subsequent reintroductions, showed that adherence to diet decreases with time [25]. In a recent survey, factors associated with nonadherence included diet effectiveness and diet-related anxiety [64]. In addition, social situations including attending public events, the need to eat in the workplace, and the lack of organization for the preparation of meals have consistently shown to impair adherence to diet, especially in the long-term [17].

When considering dietary restrictions, the burden on the QoL should also be taken into consideration. It is well known that EoE is associated with a decreased QoL, and that disease-related anxiety impacts on symptoms severity [65,66]. In this regard, although the overall QoL scores of adult EoE patients are similar regardless of treatment, patients undergoing dietary restrictions have been shown to have worse emotional impact compared to patients undergoing other treatments [67]. Additionally, being under an empiric elimination diet has been shown to be associated with a worse perception of individual QoL [67].

The impact of elimination diets on individual psychology and functioning may be more cumbersome for children with EoE. For instance, the use of elemental diets in children with EoE has been associated with a delayed onset of oral motor skills [17]. Furthermore, the disruption of feeding skills during early childhood, which may be related to sensory, behavioural, communication, and emotional skills, can result in nutritional deficiencies, faltering growth, and a significant impact on QoL [68,69]. Another concern in the context of dietary restrictions in children is the risk of avoidant/restrictive food intake disorder (ARFID). ARFID is an eating disorder characterized by failure to meet one's nutritional needs due to the fear of aversive consequences from eating [70]. Of note, ARFID may develop in patients with achalasia and coeliac disease due to the negative experiences related to feeding and the subsequent onset of gastrointestinal symptoms [70]. Recently, it has been reported that ARFID may develop in pediatric EoE patients following highly restrictive dietary regimens [71]. Of particular note, feeding-related symptoms and consequent food avoidance strategies are associated with negative psychosocial outcomes such as depression, anxiety, and worsening of social functioning [70].

Based on available evidence, efforts should be put in place for the logistic, nutritional, and psychological support of EoE patients undergoing food elimination diets to mitigate the known risks and maximize the benefits of the dietary treatment.

6. Future directions: where are we going

A recent study showed that patients with EoE who were primary non-responders to PPI treatment could be effectively maintained in histological remission with a second course of PPI following induction of remission with topical steroids [72]. The study suggested that hybrid treatment strategies could be useful in patients with EoE. In this regard, in a study by Heine and colleagues, pediatric patients with active EoE were randomized to either a combined therapy with omeprazole + FFED or omeprazole monotherapy. The authors found that, in the per-protocol analysis, significantly more patients in the combined therapy group had <10 eos/HPF at 8–12 weeks compared to patients undergoing PPI monotherapy (88% vs 45%, respectively; $p = 0.002$). However, there was a higher rate of non-completers in the combined treatment group. Therefore, in the intention-to-treat analysis, the efficacy of the two treatment was comparable, although the statistical significance was almost achieved (69% vs 44%, respectively; $p = 0.05$) [73]. Similarly, in another retrospective study, children with EoE undergoing concomitant dairy-free diet + PPI therapy responded to treatment significantly better than those who underwent dairy-free diet monotherapy [74].

Another relevant aspect that will increasingly be taken into account, as the prevalence of EoE grows, is the economic burden of the management of the disease. It is now recognized that health-care related costs in patients with EoE largely exceed those of patients with IBD and celiac disease [75,76]. In the setting of the dietary management, numerous endoscopies with biopsies are required during the reintroduction phases [27]. In an attempt to improve patients' comfort and to reduce the number of endoscopies required during the follow-up, novel non-endoscopic monitoring strategies are being investigated. In a recent study, Alexander and colleagues [77] assessed the utility of an esophageal swallowed sponge compared to biopsies to guide food reintroduction in EoE. Responders to SFED underwent food reintroduction followed by endoscopy with biopsies and sponge cytology. At the post food reintroduction evaluation, histology and sponge cytology were in agreement in 68% of patients (15/22) when using a cut off of <6 eos/HPF to define remission [77]. In another study, Ackerman and collaborators found that the levels of eotaxin-3 captured using a 1-h esophageal string test (EST) distinguished active from inactive EoE with an area under the curve (AUC) of 0.84 [78]. In addition, around 90% among patients and families, declared to prefer the EST over endoscopy if it provided similar information. More recently, eosinophil peroxidase (EPX) staining on Cytosponge samples positively correlated with the number of eos/HPF on esophageal biopsies and the EoE histologic scoring system. Of note, EPX staining on Cytosponge identified subjects with active EoE with an AUC of 0.86 [79]. In addition, a very recent study evaluating microbiota composition from salivary samples collected in 29 EoE patients and 20 non-EoE controls, showed that salivary metabarcoding analysis in combination with machine learning approaches could become a valid, cheap, non-invasive test to segregate between EoE and non-EoE patients [2]. Finally, it is known that, in patients with EoE, food sensitization on skin prick test (SPT) and measurement of serum levels of immunoglobulin E do not accurately correlate with individual trigger foods [54,80]. Recently, it has been shown that the injection of allergen extracts directly into the esophagus (i.e., esophageal prick test) could induce a local response in patients with EoE but not in controls [81]. However, whether local esophageal responses to food antigen challenges correlate with trigger foods in patients with EoE remains to be established.

7. Conclusion

Food elimination diets represent the only drug-free alternative for the treatment of EoE. Although several dietary regimens are currently available, the choice of the diet depends on individual patients' characteristics and availability of resources. A good management plan, a baseline assessment, and a rigorously scheduled follow-up of patients represent a mainstay for the success of food elimination diets in the long term. A step-up empiric elimination diet, preferably starting from a cow's milk elimination diet, should be preferred to a top-down strategy to reduce the number of endoscopies required and the time that patients spend to identify trigger foods. Novel less restrictive diets and monitoring strategies are being investigated and will likely be available in clinical practice in the foreseeable future. Novel dietary strategies should be designed to improve diet adherence, patients' satisfaction, and mitigate the drawbacks of large dietary restrictions.

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Declaration of competing interest

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