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REVIEW

Update on dietary therapy for eosinophilic esophagitis in children and adults

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ABSTRACT

Introduction: Eosinophilic esophagitis (EoE) is a chronic inflammatory esophageal disease triggered predominantly, but not excusively, by food antigens. Elimination diet thus remains the only therapy targeting the cause of the disease. Importantly, EoE is a unique form of non-IgE mediated food allergy, largely dependant upon delayed, cell-mediated hypersensitivity.

Areas covered: A comprehensive review of literature to summarize and update the most relevant advances on dietary therapy for pediatric and adult EoE patients is conducted.

Expert commentary: None of the currently available food allergy tests adequately predict food triggers for EoE, especially in adults. Elemental diet (exclusive feeding with aminoacid-based formulas) and empiric six-food elimination diet, withdrawing cow´s milk, wheat, egg, soy, nuts and fish/seafood for 6 weeks, have consistently shown the best cure rates. However, their high level of restriction and need for multiple endoscopies (top-down approach) have been a deterrent for patients and physicians. Less restrictive empiric schemes, like a four-food (animal milk, gluten-containing cereals, egg, legumes) or a two-food (animal milk and gluten-containing cereals) elimination diet have lately shown encouraging results. Therefore, a novel step-up strategy (2–4-6) may enhance patient uptake and promptly identify most responders to empiric diets with few food triggers, besides saving unnecessary dietary restrictions and endoscopic procedures.

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1. Introduction

Eosinophilic esophagitis (EoE) is a chronic, immune/antigen-mediated disease, isolated to the esophagus, characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation [1]. Since its initial description in the early 1990s [2,3], EoE has become an emerging cause of esophageal symptoms worldwide, especially in westernized countries. A recent meta-analysis has estimated the pooled incidence rate of EoE to be around 7 cases per 100,000 inhabitants-year, whereas prevalence rates ranges between 13 and 56 cases per 100,000 inhabitants [4]. Increased disease awareness along with diagnostic advances, like the Endoscopic Reference Score, has enhanced active case finding of EoE by clinicians and endoscopists [5–8].

In 1995, a seminal report showed complete reversal of refractory EoE, theoretically attributed to gastrointestinal reflux disease, in eight children after being fed exclusively with elemental diet for 6 weeks [9]. Since then, it is well established that EoE is an allergic disease predominantly, but not exclusively, triggered by food allergens. Food allergy is defined by a recurrent and predictable immune response upon ingestion of a food antigen. The mechanism of food allergy can vary from immediate immunoglobulin E (IgE)-mediated hypersensitivity to chronic autoimmune reactions driven by antigen-specific T cells. The pathogenesis of EoE, however, appears to depend largely upon delayed, cell-mediated hypersensitivity [10]. These features make EoE a distinct and unique form of food allergy, in which current blood and skin testing for food allergy are suboptimal to predict causative foods in EoE, especially in adult patients [11]. Empiric elimination diets, which consist of eliminating the most common food groups known to trigger EoE, have become the standard in clinical practice when dietary therapy is chosen. This review aims to update and summarize the most relevant data information on dietary therapy for pediatric and adult EoE patients.

2. EoE: a unique distinct form of food allergy

EoE is believed to be a Th2-cell-mediated immune response (involving interleukin [IL]-4, IL-5, and IL-13) to food and/or environmental allergens. IL-5 promotes selective expansion of eosinophils in bone marrow and their release into the circulating blood, while IL-13 stimulates the esophageal epithelium to produce eotaxin 3 – a potent chemokine that recruits eosinophils into the esophagus [10,12]. Activated eosinophils release multiple factors that promote local inflammation and tissue injury, including proteases including in their cytoplasmatic granules and transforming growth factor β. This key mediator of tissue remodeling, including subepithelial fibrosis and epithelial proliferation, can also cause smooth muscle dysfunction. In addition to eosinophils, other

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inflammatory cells, including T cells, mast cells, basophils, and natural killer cells, are also involved [10,12–15].

Even though IgE sensitization to food/airborne allergens is higher in EoE patients [15,16] and IgE-mediated mechanisms were first explored, disease induction and/or propagation are not IgE mediated, as recently proposed by an international panel of allergists and immunologists [10]. Omalizumab, an anti-IgE monoclonal antibody, has shown no benefit for treating pediatric and adults EoE patients [17,18]. Esophageal tissue from two EoE patients who had an esophagectomy displayed in a recent study granular deposits of IgG4 and abundant IgG4-containing plasma cells [19]. The authors suggested that EoE in adults may be IgG4-mediated rather than IgE-induced allergy. It is important to stress, however, that current guidelines and consensus on allergy testing do not recommend testing IgG4 antibodies [1,10].

In addition, EoE has developed after resolution of IgE-mediated allergy to a specific food (milk, egg, peanut) or aeroallergen (pollen) with oral immunotherapy [20–22]. These case reports hint at the possibility of EoE developing after a switch from an IgE-mediated allergy to an IgG4-mediated allergy. Thankfully, the first meta-analysis has lately shown that recent onset EoE occurs in 2.7% of the patients undergoing oral or sublingual immunotherapy for food allergy [23].

3. Dietary therapy

Currently, there are three major modalities of dietary therapy for EoE: elemental diet, empiric elimination diet, and food allergy testing-guided elimination diet. Elemental diet remains the most effective (90%) for both children and adults, but it seems unfeasible for clinical practice [11]. Food allergy testing-guided elimination diet has shown poor consistent result in adult studies and results seem to be better in children, although most results come from one single center. Finally, empiric elimination diet has consistently demonstrated a 72% effectiveness overall for pediatric and adult patients, but optimization strategies to reduce the level of restriction and number of endoscopies are currently underway. Effectiveness rates for all these three dietary interventions in children and adults are summarized in Figure 1.

3.1. Elemental diet

As aforementioned, the ability of dietary modifications to induce remission of EoE was initially demonstrated in 1995, in a pioneering pediatric series with refractory esophageal eosinophilia attributed to gastroesophageal reflux [9]. Ten children were exclusively fed with an elemental formula, in which all proteins are eliminated and the nitrogen source is exclusively provided by single amino acids, thus devoid of antigenic capacity. All patients normalized the esophageal histology; eight of them (80%) exhibited complete clinic remission after at least 6 weeks on an elemental diet and the remaining two clinical improvement. Elemental diet has been shown to induce clinical improvement after only 8.5 ± 3.8 days [24], while achieving histological remission in around 2 weeks

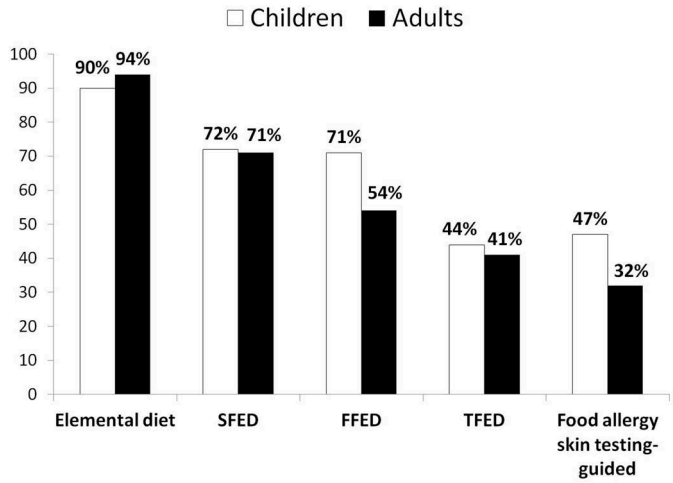

Figure 1. Histologic remission rates for the three most common dietary interventions (elemental, empiric, food allergy skin testing-guided) in children and adults.

[25]. Overall effectiveness in a recent meta-analysis was consistently close to 90% in both children and adults [11]. However, this dietary strategy seems unfeasible in clinical practice due to a variety of reasons, including its poor palatability (requiring nasogastric tubes in most children), lack of adherence, social and quality-of-life impairment related to complete avoidance of all kind of table food, and their high cost, not universally covered by health systems or insurances.

A potential role for elemental diet has been proposed after failure to conventional therapy, either topical steroids or empiric six-food elimination diet (SFED), in patients who wish to remain in remission while investigating the casual role of unusual foods and aeroallergens in their disease, but this approach remains to be evaluated yet [26].

3.2. Food allergy testing-guided elimination diet

Food allergy testing-guided elimination diet stands for eliminating foods with positive results on skin prick test (SPT) and atopy patch test (APT). SPT is intended to measure immediate hypersensivity to food, whereas APT will measure delayed food hypersensitivity. A first report on the effectiveness of this strategy coupling SPT and APT showed clinic and histologic remission in 49% of pediatric patients [27]. Mean age of patients was 5 years old and five food groups on average were eliminated per patient. The main criticism to this study is that food triggers were not identified by histological remission, but rather symptom relapse after individual food reintroduction [27], as reported by parents. Likewise, APT is not standardized for clinical practice. The same research group from Philadelphia updated their results in 2012 with an overall effectiveness of 53% [28]. When cow's milk was systematically eliminated, regardless of SPT/APT results, and elemental diet was instituted in patients with diets felt to be too restrictive, the effectiveness rose up to 72% [28]. These results have not been replicated in other studies conducted in pediatric [29,30] and adult [31–34] patients. A recent meta-analysis revealed that this dietary approach led to histologic remission in

45.5% of patients (95% CI, 35.4–55.7%), with wide heterogeneity (I^2: 75%) indicating a low reproducibility [11]. Noteworthy, its effectiveness was significantly lower in adults when compared to that found in children (32.2% vs. 47.9%) [11].

As for the accuracy of SPT and APT to detect the most common causative foods in EoE (cow's milk, wheat, and egg) in children, negative predictive values (NPVs) for food allergy skin testing are generally superior to positive predictive values (PPVs) in EoE patients. Diagnostic accuracy of food allergy skin testing in pediatric EoE in Philadelphia has shown variable PPV for SPT ranging from 26.3% to 86.3% (average 47%), while NPV was >90% for multiple foods, with the exception of the most common EoE food triggers [cow's milk (30%) and egg, wheat, and soy (79–90%)] [27]. Likewise, results for APT followed a similar trend, with PPV ranging from 12% to 86.2% (average 44%), and NPV >90% with the exception of milk (31%). The combination of SPT and APT yielded an averaged PPV poor (44%) but increased the average NPV (92%), with the exception of milk (44%) [28]. However, other pediatric research groups have found lower NPVs for milk (40%), egg (56%), and wheat (67%), the most common food triggers in EoE [30].

Regarding adult patients, an extremely low concordance between food allergy skin testing results and food triggers of EoE identified by biopsy-monitored sequential food reintroduction has been repeatedly provided [31–34]. Beyond skin testing, a pilot study in adult patients evaluated the effectiveness of a serum IgE microarray-guided elimination diet, but the study was early interrupted due to poor efficacy (7% histologic remission rate) [35]. Finally, a recent study comprehensively assessed the accuracy of combining five different skin and blood food allergy tests to detect offending foods in adult EoE patients [36]. None of the evaluated food allergy tests, measuring IgE and non-IgE hypersensitivity to foods, could accurately predict food triggers identified through food challenge with histologic reassessment in responders to a SFED [36].

Overall, cumulative data support the current thought that EoE is primarily non–IgE mediated, mainly associated to IgG4, in which using food allergy serum or sking testing is discouraged in adults and, at the very least, questionable in children [1,10]. Aside from methodological issues, discrepancies between children and adults hint at the possibility of EoE switching from an IgE type allergy to an IgG4 type allergy as patients become adult, but this remains to be elucidated.

3.3. Empiric elimination diet

3.3.1. SFED

Aiming at overcoming unfeasibility of elemental diet in clinical practice and the low sensitivity/specificity of food allergy skin testing, an empiric elimination diet was first tested in pediatric EoE patients from Chicago in 2006 [37]. This diet was termed SFED and consisted of eliminating for 6 weeks the six-food groups most commonly associated with food allergy in the pediatric population in Chicago (cow's milk protein, wheat, egg, soy, peanut/tree nuts, fish, and seafood). A SFED led to clinic and histologic remission in 74% of children in this first seminal study, being not inferior to elemental diet [37]. Similar results have been further obtained in patients of all ages [11]. A first meta-analysis recently disclosed that after inclusion of seven observational studies, a SFED provided an extremely homogenous (I^2 statistic = 0) histologic remission rate of around 72% (95% CI, 66–78%) in both children and adult patients [11]. The effectiveness and wide reproducibility of a SFED are counteracted by several drawbacks, like the high level of dietary restriction and the large number of endoscopies after individual food reintroduction. 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 endoscopies [32–34,36,38,39,40] (Table 1).

3.3.2. Four-food elimination diet

The most common causative foods identified after a response to a SFED have been cow's milk, wheat, egg, and, to a lesser extent, soy/legumes, with a negligible role for nuts, fish, and seafood. Consequently, an empiric elimination diet avoiding the four most common food triggers in EoE (milk, wheat, eggs, and legumes), the four-food elimination diet (FFED), was developed. A first prospective multicenter study in adult patients showed a 54% remission in adults [39], whereas an abstract in pediatric population revealed a 71% efficacy [41]. In both studies, cow's milk was the most common food trigger (especially in children). Half of adult responders were found to have cow's milk, wheat, or both as food triggers, whereas 74% of pediatric patients had a single food trigger [39,41].

3.3.3. Step-up approach: TFED, FFED, SFED

Accordingly, a step-up approach (in other words, eliminating at first the one or two most common food triggers and subsequently increasing the level of restriction in nonresponders) should be further evaluated in EoE. An upcoming study, only available in abstract form, has first evaluated the efficacy of a two-food elimination diet (TFED) (animal milk and gluten-containing cereals), stepping up to FFED and SFED in nonresponders [42]. A TFED achieved EoE remission in 38 patients (40%), whereas remission rates increased to previously known rates with a FFED and SFED, respectively. Up to three quarters of responders to a TFED showed a single food trigger, being the most common animal milk (60%), gluten-containing cereals (25%), and both (15%) [42]. Compared to starting with a SFED, this step-up strategy allowed reducing endoscopic procedures and the diagnostic process time by up to 35%. The most common food triggers identified in empiric elimination diet studies (either TFED, FFED, or SFED) are shown in Table 1.

3.3.4. Cow's milk elimination diet

Since cow's milk has been reported the most common food trigger in both children and adults, cow's milk elimination diet would be a first easier way to check the efficacy of dietary intervention. Cow's milk wheat elimination diet in children has been recently reported in two studies [43,44]. Despite encouraging results (65% [43] and 61% [44]), both studies are flawed by methodological issues. In the first one, included patients were those suffering from IgE-mediated cow's milk food allergy after cow's milk oral desensitization [43]. Aside from not being representative of a standard

Table 1. Summary of the results of prospective studies on empiric six- (SFED), four- (FFED), or two- (TFED) food group elimination diets, showing the number and the most common food triggers identified through individual food reintroduction.

First author, year of publication, country, reference	Diet Population Design Sample size	Histologic remission (%)	Number of culprit foods identified through individual reintroduction of either six, four, or two food groups			Most common food triggers identified through individual food reintroduction
			1 (%)	2 (%)	>2 (%)	
Kagalwalla, 2011, US [37]	SFED Children Unicenter 35	74	72	8	8	Milk 74% Wheat 26% Eggs 17%
Gonsalves, 2012, US [32]	SFED Adults Unicenter 50	70	85	15		Wheat 60% Milk 50%
Lucendo, 2013, Spain [33]	SFED Adults Unicenter 67	72	36	31	33	Milk 62% Wheat 29% Egg 26% Legumes 24%
Wolf WA, 2014, US [34]	SFED Adults Unicenter 22	56	66		33	Milk 44% Egg 44% Wheat 22%
Rodriguez-Sanchez, 2014, Spain [38]	SFED Adults Unicenter 17	53	–	–	–	Milk 64% Wheat 28% Egg 21% Legumes
Molina-Infante, 2014, Spain [40]	FFED Adults Multicenter 52	54	45	45	–	Milk 50% Egg 36% Wheat 31% Legumes 18%
Kagalwalla, 2015, US [41]	FFED Children Multicenter 55	71	74	21	5	Milk 68% Egg 26% Wheat 21%
Philpott, 2016, Australia [36]	SFED Adults Unicenter 29	52	56	17	13	Milk 43% Wheat 43% Eggs 34%
Molina-Infante, 2016, Spain [42]	TFED Children and adults Multicenter 124	42	75	25	–	Milk 65% Milk and wheat 20% Wheat 15%

SFED: Six-food elimination diet.

population of pediatric EoE, cow's milk oral immunotherapy-induced EoE has been always shown to be responsive to cow's milk elimination diet [23]. As for the second study, proton pump inhibitor (PPI) was concomitantly given to dietary therapy. A recent meta-analysis disclosed that up to 50% of pediatric and adult patients can achieve EoE remission with PPI alone [44]. Therefore, combining two different therapeutic assets for EoE makes it hard to discern how many of these patients would have actually achieved remission on PPI therapy alone.

4. Practical considerations for food reintroduction after response to empiric diets

Practical tips for dietary management in EoE patients are summarized in Table 2. All dietary treatment strategies are intended to induce EoE remission, as a starting point for subsequent identification of potential food triggers. The ultimate goal is to exclude from the diet just food(s) responsible for triggering and maintaining the disease in each individual patient. For this purpose, once remission of eosinophilic inflammation is achieved with an empiric diet, individual reintroduction of food or food groups one at a time should be undertaken for a minimum of 6 weeks. Consuming a previously excluded food after obtaining histological remission of EoE constitutes a food challenge test, which represents the gold standard for the diagnosis of food allergies [45]. Documentation of food triggers requires an endoscopic procedure after each food reintroduction. Once all eliminated food or food groups have been individually reintroduced, identified food triggers should be removed indefinitely from the diet, whereas foods which do not trigger inflammation and are well tolerated can be consumed regularly.

The dissociation between clinical symptoms and histology in EoE has been repeatedly documented in children and adult [46,47], implying that the absence of symptoms after food reintroduction does not necessarily mean disease remission [47]. Due to lack of noninvasive biomarkers that may adequately predict the presence or absence of esophageal eosinophilic inflammation [48], multiple endoscopies with systematically performed biopsies are currently mandatory to accurately identify food triggers. Acceptance of this strategy and reuptake of patients is largely conditioned by systematic sedation for endoscopic procedures, along with flexibility to

Table 2. Practical tips for dietary therapy in EoE.

(1) Due to convenience, cost and safety profile consider PPI therapy in EoE patients before either topical corticosteroids or elimination diets
(2) Ponder cautiously any elimination diets for patients already on multiple dietary restrictions due to IgE-mediated food allergy. Severe symptomatic patients may benefit best from topical corticosteroids. Compliance issues with diets may arise in older children, adolescents, and young adults
(3) Elemental diet is unfeasible in clinical practice and should be exclusively reserved for refractory patients
(4) Food allergy skin and blood testing-guided diet is discouraged for adult patients. Its efficacy is variable in children, with conflicting results in literature
(5) Efficacy rates for empiric elimination diets are consistent between children and adults. Cow's milk, wheat, and eggs are the most common food triggers of EoE in children and adults from the United States, Spain, and Australia
(6) A step-up approach for empiric elimination diets might be cost-effective and improve patient uptake for dietary therapy. Therefore, a six-food elimination diet must be reserved for highly motivated patients unresponsive to a two- or four-food elimination diet
(7) All diets should be followed for a minimum of 6 weeks. Its efficacy should be evaluated through symptoms and inflammation improvement in esophageal biopsies obtained during an endoscopic procedure. Sedation for endoscopic procedures is key to engage patients with empiric elimination diets
(8) After remission eliminating several foods or food groups, foods should be individually reintroduced while continuing on the diet (one at a time) for a minimum of 6 weeks, with an endoscopic procedure after each individual food reintroduction
(9) The final goal is to identify which food trigger esophageal inflammation and which do not, in order to design an individualized diet for each patient, avoiding exclusively causative foods in the long run
(10) When available, dietary counseling should be considered for patients on elemental diet, six-food elimination diet, and patient responders to empiric diets with long-term avoidance of multiple food triggers

schedule and reschedule endoscopic appointments every 6 weeks, depending on histologic results.

5. Expert commentary

Dietary therapy has steadily become accepted as a valid therapy for EoE patients, along with pharmacological treatment. Due to its high efficacy [49], low cost, and safety profile, it is important to stress that we always choose PPI therapy as the first-line therapy for a patient with symptoms and histologic features compatible with EoE. Exceptions to this rule might be patients unwilling to take any medications or severe symptomatic patients with fibrostenotic features who will likely benefit best from topical corticosteroids. Only once the patient is confirmed to be unresponsive to PPI therapy, a thorough discussion with the patients and/or their parents should be undertaken to decide what next therapeutic step to take, considering the advantages and disadvantages of dietary manipulation. Some important factors may influence our decision as well, including previous food allergies (patients already on restrictive diets due to food allergies are generally poor candidates for dietary therapy with additional dietary exclusions), patient age (older children, adolescent, and young adults usually poorly comply with dietary restriction for EoE), and patient/family preferences.

Regarding diets, we reserve elemental diet exclusively for difficult-to-treat refractory cases. Likewise, we actively discourage food allergy testing in adult EoE patients for the specific purpose of identifying food triggers. The efficacy of skin and blood testing in children is controversial and results in literature are conflicting [11]. Currently, our favorite dietary strategy is an empiric TFED (animal milk, gluten-containing cereals) or FFED (animal milk, gluten-containing cereals, egg, legumes). After following the diet for a minimum of 6 weeks, symptoms are assessed and a repeat upper endoscopy with esophageal biopsies is performed at the end of the initial avoidance period. If clinicohistologic remission is accomplished (at least <15 eos/HPF), then foods are reintroduced while on the empiric diet one at a time for a minimum of 6 weeks, with an endoscopic procedure after each individual food reintroduction to determine which do and do not trigger the disease. This cumbersome sequence is key to design a long-term maintenance diet, avoiding solely causative foods that objectively trigger the disease. Until novel food allergy testing is available, novel minimally invasive diagnostic tools to measure esophageal mucosal inflammation, like the string test or the cytosponge [50,51], show promise to minimize the number of endoscopic procedures. We usually first reintroduce wheat, since if it is not proven to trigger esophageal inflammation, might be indefinitely reintroduced during food reintroduction in order to minimize food restrictions and normalize quality of life and socialization.

A detailed comparison between the proposed step-up [42] and the top-down [52] approaches is displayed in Table 3. By using this empiric step-up TFED to FFED, responders will be on highly restrictive diets for a maximum of 18 and 30 weeks, including the index endoscopy and subsequent individual food reintroductions. A dietitian is not necessary to undertake a 6-week TFED (they can eat meat, fish, egg, legumes, and all kind of fruit and vegetables) and likely can be obviated for a FFED, with a good education on food labeling of gluten-free products. Therefore, we do not consider mandatory dietary counseling for this approach. Compared to a SFED, this step-up approach reduces by 20% time on unnecessary dietary restrictions and endoscopic procedures [42]. The most important addition of this therapeutic step-up approach is a prompt recognition of two-thirds quarters of patient responders to a SFED with one single endoscopy. In addition, most of these patients will have one or two food triggers after identified after individual food reintroduction [42]. This subset of patients is the best candidates for maintenance dietary therapy. By using this step-up approach, it has been shown that the higher the level of restriction, the higher likelihood of having more food triggers [42]. As such, we usually reserve a SFED for motivated patients unresponsive to a TFED and FFED still willing to elucidate their food triggers. Most likely, a dietitian might be advisable in this specific subset of patients due to the high level of restriction in these patients, especially in responders which will go through a 52-week food reintroduction process. The use of the empiric elimination diet has brought up a number of issues regarding avoidance of specific foods versus food groups. Both cross reactivity and different geographical patterns of food consumption among countries may account for these discrepancies. As for dairy products, Spanish investigators do not eliminate only cow's milk, but also sheep's and goat's milk, which are frequently consumed

Table 3. Comparison of top-down (starting with a SFED) and step-up (starting with a TFED and then stepping up to a FFED and eventually to a SFED) approaches for dietary therapy in EoE.

	Top down	Step up
Definition	A SFED is offered as the only empiric elimination diet	A TFED is offered as the initial dietary therapy. In nonresponders, a stepping up to FFED or SFED is offered
Initial effectiveness SFED vs. TFED	72%	40% (almost two-thirds of responders to a SFED)
Initial dietary restrictions	Milk, wheat, egg, legumes, nuts, fish, and seafood	Milk and wheat
Number of endoscopic procedures in responders to the initial diet	Seven endoscopic procedures Index +1 per food eliminated	Three endoscopic procedures Index +1 per food eliminated
Duration of dietary restrictions in responders	42 weeks without wash-out periods	18 weeks without wash-out periods
Identified food triggers after individual reintroduction	65–85% have one or two food triggers	70% have a single food trigger and 100% one or two food triggers
Calculations in terms of endoscopic procedures and time on dietary restrictions for each approach in 10 consecutive EoE patients	SFGED 52 Endoscopic procedures 312 weeks	TFGED + FFED + SFED 42 Endoscopic procedures 242 weeks

TFED: Two-food elimination diet; FFED: four-food elimination diet; SFED: six-food elimination diet.

with cheese [33,39,42,38]. While initial studies did wheat elimination only, international practitioners and Spanish researchers are currently to eliminate all gluten-containing grains (wheat, rye, barley) [53]. In addition, while most US clinicians recommend avoidance of only soy, Spanish investigators tend to recommend avoidance of all legumes, since lentils, chickpeas, and beans are often consumed in Mediterranean countries [33,39,42,38].

6. Five-year view

6.1. New food allergy tests for EoE

Undoubtedly, better food allergy testing is clearly warranted to adequately detect the causative foods in EoE. We have learned two major lessons over the past 10 years: first, that elevated levels of local IgG4, rather than IgE, may be implicated in disease pathogenesis; and second, that skin and blood reactivity do not predict what eventually happens locally in the esophagus. A first attempt to overcome these hurdles has been recently published in a small exploratory study [54]. Food-specific IgG4 in esophageal tissue was significantly overexpressed in 20 EoE patients compared to controls, confirming that an antigen-specific IgG4 response may contribute to the pathogenesis of EoE. These differences were not observed in blood samples. However, no differences in food specific IgG4 were observed between diet responders (n = 11) and nonresponders, likely related to small sample size [54]. Further studies evaluating this hypothesis are currently underway. Whether direct food injection in esophageal epithelium can positively predict EoE food triggers remains unproven but merits further research. This provocative conjecture, however, may be dependent on food dosing and timing of exposure. Accordingly, a single injection or endoscopic procedure may not suffice to induce EoE and repeat endoscopy might be required.

6.2. Long-term efficacy and safety of dietary therapy

Once food triggers responsible for EoE in each individual patient have been identified, long-term avoidance is advisable in order to maintain drug-free disease remission. This issue, however, has not been addressed in literature yet. Indirect data come from clinical observations in studies evaluating the short-term efficacy of empiric and guided diets. Three studies conducted in adults [32,33,40] have consistently reported that all compliant patients who strictly avoided food(s) known to trigger the disease remained on clinic and histologic remission for a period of up to 3 years [33]. Regarding children, studies rechallenging five patients after effective long-term avoidance of food triggers (up to 4 years) demonstrated EoE recurrence in most of cases [40]. Empiric SFED therapy has shown no treatment-related complications and none of the children exhibited nutrient deficiencies or growth deceleration during the dietary reintroduction phase [40] or even after a year of progressive reintroduction of eliminated foods [55]. No study has appropriately evaluated the long-term effects of long-term food avoidance on the natural history of EoE, especially regarding the reversion of fibrous remodeling phenomena, neither the impact on the health-related quality of life of EoE patients.

6.3. Why staple foods for milenia (milk, wheat, and eggs) trigger now EoE in westernized countries?

We have now a new allergic disease, first reported in 1993 [2], know to be triggered by staple foods for milenia, such as cow's milk, wheat, and eggs. This disease predominantly affects children and young adults, peaking between 35 and 45, and then the prevalence sharply decreases in patients over 50 years old [56]. Rather than genetic changes in such a short period of time, it is temptative to speculate whether something might have changed in the environment 20–30 years ago that began to affect children born after that time but did not affect older individuals. Currently, it remains unknown whether changes in food sources, addition of antibiotics/fertilizers, genetic modifications to plant and animal foodstuffs, drastic accelerated processing of food supplies, and plastic or synthetic food packaging may account for causality and merit further research [56]. Being wheat the second most important allergen in EoE (a Th2-mediated disease), it is interesting to speculate whether the aforementioned mechanisms regarding food changes may play a role of other emerging wheat-related

disorders affecting children and adults, like celiac disease (a Th1-mediated disease) on non-celiac wheat sensitivity (innate immune response) [57].

6.4. Will we witness EoE triggered by similar or different foods in developing countries?

Large numbers of EoE cases have been reported in North America, Western and Eastern Europe, and Australia. Fewer cases have been reported in South America, Asia, and the Middle East; cases from Northern Africa have been recently reported [58], and, as of yet, none in sub-Saharan Africa or India [56]. This epidemiological trend clearly suggests at least a partial implication of the hygiene hypothesis as a major modulator of the disease. With the advent of globalization, many developing countries are turning to a westernization of their life habits, including more hygiene measures and reduction of traditional foods (e.g. rice in South America and Asia) in favor of wheat-containing fast food sources. Whether this trend will eventually result in a demographic explosion of EoE cases in developing countries should be monitored. Likewise, whether EoE might be triggered by different staple foods established for milenia in other geographical areas (e.g. fish in Japan, seafood in Asia) also merits further investigation.

7. Key issues

- Eosinophilic esophagitis (EoE) is a unique, complex and different form of food allergy, with a predominant non IgE-mediated local inflammatory response,
- EoE is triggered mainly, but not exclusively, by food antigens. Unlike pharmacological therapy, dietary therapy is the only treatment targeting the cause of EoE and not the inflammatory consequences of the disease.
- Dietary therapy is not a panacea. Up to 10% and 30% will not respond to an elemental diet and a six-food elimination diet, respectively. Airborne allergens themselves or cross reactivity with food antigens may be responsible for refractory cases.
- Elemental diet is the most effective dietary intervention, but it is unfeasible in clinical practice. This strategy should be reserved for difficult-to-treat refractory patients.
- None of the available food allergy testing, either in skin or blood, can adequately predict the causative foods triggering EoE, principally in adult patients.
- An empiric six-food elimination diet (SFED) has been key to identify the causative foods linked to EoE patients. Cow's milk, wheat and eggs have been consistently reported to be the most common food triggers in Europe, United States and Australia.
- A SFED is currently hindered by its high level of restriction and large number of endoscopies. A SFED should be currently reserved for highly motivated patients unresponsive to easier empiric dietary interventions.
- An step-up approach (two- and four-food elimination diet), avoiding the most common food triggers, will likely be recommended as a first-line strategy in the dietary management. Likewise, this paradigm shift will likely foster further engagement of patients and physicians with diets in EoE patients.

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Declaration of interest

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