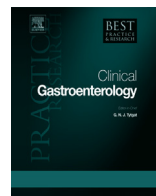




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Elimination and elemental diet therapy in eosinophilic oesophagitis



M.J. Warners, MD ^a, B.J. Vlieg-Boerstra, PhD RD ^b,
A.J. Bredenoord, MD PhD ^{a,*}

^a Department of Gastroenterology & Hepatology, Academic Medical Centre, Amsterdam, The Netherlands

^b Department of Respiratory Medicine and Allergy, Emma Children's Hospital, Academic Medical Centre, Amsterdam, The Netherlands

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Eosinophilic oesophagitis (EoE) is a chronic immune-mediated disorder of the oesophagus. The incidence of EoE has been raised substantially and EoE has recently become the most prevalent cause of dysphagia among the adolescents. Food and aeroallergens are believed to play a major role in the pathogenesis. Current treatment includes topical steroids and dietary therapy. Dietary therapy with elimination of causative allergens could provide a durable long-term solution. Dietary therapy in EoE consists of in elemental and empiric elimination diets. Elemental diet with amino acid-based formula is most effective in achieving disease remission but poor taste makes adherence challenging. Empiric elimination diet based on avoidance of most common food allergens offers moderate response rates, the usefulness of allergy test-directed elimination diets is questioned by low response rates. In conclusion, dietary treatments for EoE seem promising, but further refinement is required before it can become standard care.

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* Corresponding author. Department of Gastroenterology & Hepatology, Academic Medical Centre, PO Box 22660, 1100 DD Amsterdam, The Netherlands. Tel.: +31 20 566 55 84; fax: +31 20 691 70 33.

E-mail address: a.j.bredenoord@amc.uva.nl (A.J. Bredenoord).

Introduction

Although the pathophysiology of EoE is not fully understood, it appears to partly align with other atopic diseases such as asthma and atopic dermatitis [1]. Food and aeroallergens are believed to play a major role in the pathogenesis of EoE [2]. Recently published data showed that an impaired oesophageal epithelial barrier function allows permeation of molecules with the size of food and aero-allergens, potentially activating a Th2 immune response in predisposed individuals [3]. The concept of EoE being an allergic disease activated by food allergens is further supported by the notion that EoE can be driven into remission by dietary treatment [4,5].

EoE has been clinically linked to allergy because most patients present with concurrent atopic disorders [6]. Furthermore, seasonal variation of disease activity, with an increase during pollen season, suggests aeroallergen involvement [7]. Clinical observations had been invigorated by experimental research, showing that exposure to food allergens can induce eosinophilic oesophageal inflammation in animal models [8]. Furthermore, previous research observed that the oesophagus from EoE patients showed inflammatory signs that were histopathologically consistent with other atopic diseases [5]. Not only increased intraepithelial eosinophil levels were found, but also elevated levels of activated T-lymphocytes with allergy associated cytokines IL-5 and IL-13 [5]. Genetically the link between allergy and EoE is supported by an enriched expression of allergic sensitization genes in EoE patients [9].

Food-triggered immune responses can be classified as immediate IgE-mediated or as delayed non-IgE-mediated. In EoE both mechanisms may play a role. According to the non-IgE-mediated reaction, allergen uptake in the oesophagus may activate a Th2-associated immunologic pathway, causing eosinophilic oesophageal infiltration and inflammation [2,10–12]. Another key player in the inflammatory process is the mast cell, which has an important role in the IgE-mediated reaction. An increased density of IgE-bearing mast cells is found in the oesophageal tissue, and degranulation of its mediators also triggers the inflammation [13,11].

The prominent eosinophilic infiltration and inflammation of the oesophagus can cause transient narrowing of the lumen by oedema, and fixed narrowing by remodelling and fibrosis. EoE becomes endoscopically apparent as fixed rings, longitudinal furrows, white exudates, oedema and fragile mucosa, described as crepe-paper oesophagus [14].

EoE presents in adults with dysphagia and food impaction whereas children typically present with vomiting, nausea and abdominal pain [15]. EoE is diagnosed based on symptoms of oesophageal dysfunction and a threshold of more than 15 eosinophils/high-power field (eos/hpf), which is not explained by other disorders [16].

According to current ACG guidelines treatment of EoE consist primarily of topical corticosteroid and dietary therapy by which causative food triggers are restricted [17,18]. In patients with dysphagia due to irreversible fibrostenotic strictures dilatation is considered. Topical corticosteroids offer clinical and histological improvements, although response is only temporarily since the disease recurs once the corticosteroids are withdrawn. Side-effects such as candidiasis may hinder long-term treatment [19]. Dilatation became an accepted treatment in recent guidelines since the risk of perforation seems much lower than initially reported and may be as low as 0.3% [20]. Nevertheless recurrence of symptoms often occurs since the underlying inflammation is not treated. Dietary therapy with elimination of causative allergens could potentially be the most durable long-term solution, which is desirable since the majority of patients are young adults or children, and EoE is a chronic disease.

The two main modes of dietary treatment are: (1) elemental diets, consisting of amino acid-based formulas which eliminates all potential triggers, and (2) elimination diets, which can be further divided into (2a) empiric elimination diets based on avoidance of most common triggers (i.e., milk, egg, soy, wheat, peanuts/tree nuts, and fish/shellfish) and (2b) test-directed or targeted elimination diets, based on allergy test results.

In this review we will evaluate the efficacy of each dietary treatment along with its advantages and limitations in order to provide insight in dietary management of EoE.

Elemental diets

Elemental diets consist of a hypoallergenic, amino acid-based formula and are a complete source of nutrition. Amino acids do not provoke allergic reactions since their small size prevents uptake by the immune system [21]. Initially, elemental diets were developed for treatment of severe cow's milk allergy (CMA), the most common food allergy during the first years of life [22].

Over the past decades the role of food allergens in EoE became more evident, which has changed disease management strategies. The efficacy of dietary elimination with an amino-acid based formula in EoE was first reported in 1995 [4]. In this study, elemental feeding (Neocate or Neocate-I-Plus, Scientific Hospital Supplies (SHS) a subsidiary of Nutricia) was used as last resort in ten children with refractory eosinophilic inflammation. After six weeks of elemental diet patients achieved complete remission ($n = 8$) or improvement ($n = 2$) of symptoms. Histologically peak eosinophil count decreased from 41 eos/hpf to 0.5 eos/hpf after the elemental diet. This led to the hypothesis that not acid reflux, but ingested foods were the causative triggers of the eosinophilia. The influence of food allergens in the pathophysiology of EoE was confirmed by disease recurrence after food reintroduction.

Building on these first positive results, Markowitz et al. confirmed the role of food allergens as an important driver of EoE by demonstrating nearly complete response rates after elimination diet (Neocate 1+, SHS Nutricia) in children with EoE [23]. In this prospective paediatric study 96% of patients ($n = 51$) showed a significant clinical and histological response; eosinophil count reduced from 33.7 eos/hpf to 1.0 eos/hpf. The rapid observed symptom improvement was remarkable with an average of only 8.5 days. A drawback of this study was the poor tolerance of the elemental diet, leading to the need of nasogastric feeding in 48 out of 51 children. However, besides validating the efficacy of elemental diets, this study also introduced a shorter time frame to achieve histological response (four weeks), which could enhance adherence.

The next retrospective paediatric study ($n = 160$) revealed comparable results with symptom resolution and histologic normalization in 97% of children. Peak eosinophil count decreased from 38.7 eos/hpf before to 1.1 eos/hpf after elemental diets (Neocate, Neocate EO28, Neocate 1+, SHS Nutricia, and Elecare, Abbott Laboratories). In four (2.4%) patients with refractory oesophageal dysfunction and eosinophilia, non-compliance and environmental allergens might have influenced this lack of response [24]. Unfortunately, unpalatability was again the major problem, since only 20% of the children were able to ingest the formula orally.

Although there are no randomized controlled trials comparing elemental diets with other dietary treatment, Kagalwalla et al. evaluated the efficacy of elemental ($n = 25$) and empiric elimination ($n = 35$) in a retrospective observational study with two comparable cohorts [25]. Significant histological remission was seen in 88% of patients that received elemental diet (Neocate, Neocate EO28 and Neocate 1+; SHS Nutricia, or Elecare; Abbott Laboratories) versus 74% of patients receiving empiric elimination diets. Four patients, refractory to empiric elimination, eventually responded to elemental diet, which increased the complete remission rate to 90%.

Subsequently, Henderson et al. confirmed that elemental diet is superior at obtaining histologic remission compared with other dietary interventions [26]. Pairwise comparison showed significant higher response rates after elemental diets (Neocate and NeocateEO28 Splash; Nutricia or EleCare; Abbott Laboratories) compared with allergy test-directed diets (96% versus 81%, $p = 0.001$). Claiming to be the first comparative study between various dietary treatments in EoE, results should be interpreted with caution due to the retrospective study design. Patients were not randomly assigned to a diet, but in accordance with the physician, the patient, and their parents a choice was made, which could have introduced selection bias. Furthermore dietary therapies were not defined in the same manner, different amino-acid formulas were administered and both empiric and test-directed elimination diets were followed, which could preclude an accurate comparison.

The promising results of elemental diets had not been validated in adults until Peterson et al. reported the first prospective study of 29 adult EoE patients. In total, 17 patients completed a four-week elemental diet trial (EleCare; Abbott Nutrition) of which 13 patients (72%) achieved complete or near complete disease remission (<10 eos/hpf). Additionally four patients showed a 50% decline in peak eosinophil count with regard to baseline endoscopy. The response rate would have been 94.4% if results were analysed in accordance with current guidelines (remission defined as <15 eos/hpf) [15].

Surprisingly, there was no improvement in the Mayo dysphagia questionnaire. As suggested by the authors this could have led to a lower adherence rate compared to paediatric studies. Furthermore, questionnaires were filled in on the last day of the restricted liquid diet, which complicated the evaluation of dysphagia for solid foods. The high patient dropout (41%) in this study calls into question whether this treatment is very suitable in clinical practise. Although this study demonstrated that the efficacy of elemental diet is comparable in adults, further research is warranted to validate these outcomes.

Generally, the goal of elemental diet therapy in EoE is to bring patients into complete remission and subsequently identify the allergic trigger. Once remission is established, food groups are reintroduced systematically in a stepwise way and repeated endoscopies are performed to evaluate histological response. Elemental diets are used to induce rapid disease remission, since the amino-acid formula is not feasible for permanent use [27,28]. Elemental diets are thus usually combined with elimination diets.

Discussion elemental diets

The overall efficacy of elemental diets in EoE is estimated as more than 90% for adults and children [29]. Which supports the hypothesis that food triggers are the predominant cause of EoE in both groups. Its high costs, which are not always reimbursed, and poor taste are the most important limitations for widespread implementation in clinical practise. Also, elemental diets are usually combined with an elimination diet afterwards and the latter requires a substantial number of endoscopies as for each reintroduction of a food group endoscopy with biopsies is required to confirm histological response.

However, the most important pitfall of elemental diet is the poor taste of the product. Children nearly always need nasogastric feeding for delivery of the product. As for adults a major lifestyle modification is needed, which could lead to avoidance of social situations and may affect quality of life. Furthermore, nasogastric feeding and a complete fluid diet diminish chewing, which is the most efficient way to stimulate salivary flow. Saliva is essential in protecting oral health. Therefore oro-motor function and saliva production will need to be stimulated by alternative manners, such as chewing gum.

Although amino-acid based formulas provide complete nutrition, substantial weight loss has been reported in adults [30]. The nutritional state before and during the diet should be monitored carefully to prevent deficiencies and growth failure. Development of a more tolerable taste or different flavours of these formulas may overcome these difficulties and may stimulate patient's adherence.

The entire process is time consuming, therefore intensive guidance by a dietician and physician in order to motivate patients is of great importance for success. Although long-term data are scarce, continuous dietary restriction of the responsible foods seems to maintain disease remission of this emerging chronic disease [31].

Empiric elimination diets

Currently, the most frequently advised diet in EoE is the empiric six food elimination diet (SFED). The SFED allows the intake of a variety of table foods while six food groups, namely cow's milk, wheat, egg, soy, peanut/tree nuts, and fish/shellfish are eliminated [32]. These food groups have been identified as the most common food allergies in the United States for many years [32]. Milk, egg, and peanuts more frequently trigger an allergic reaction in children, whereas tree nuts and fish/shellfish account for most allergic reactions in adults [32]. Two decades ago, emerging evidence revealed that EoE was also associated with food allergy [6]. In 2005, a 10-years evaluation of dietary treatment in EoE identified the same offending food allergens for EoE as for food allergies. In a cohort of 381 patients, milk and egg allergies were seen in 45% of the patients followed by soy, corn and wheat (30%) [24]. However, most patients had multiple food allergies. Despite all the reports confirming the influence of the major food allergens, it should be noted that more than 170 different foods have been associated with allergic reactions [28]. Advantages of SFED are that it does not require allergy testing and it allows the consumption of multiple table foods. However, the food reintroduction process is time consuming

and invasive; once histologic remission is established after SFED, a food group a week will be reintroduced starting with the least allergic foods. After each reintroduction an endoscopy with biopsies is performed to evaluate histological response. Disease monitoring is restricted to histologic evaluation, as symptoms have been shown to be not reliable enough for prediction of histological recurrence.

The first publication describing SFED reported clinical and histologic improvement in 26 out of 35 (74%) paediatric EoE patients [25]. This study evaluated dietary treatment in two cohorts, one treated with SFED and one with elemental diet. After six-weeks, the peak eosinophil count decreased to less than 10 eos/hpf in 74% of the patients treated with SFED, compared to 88% of the patients in the elemental diet group. The percentage of dropouts due to dietary non-compliance was slightly higher in the elemental diet group (5% vs. 7%). Patient characteristics were highly comparable between groups [25]. Since the identification and elimination of the disease-triggering allergens is a very important aspect, a subsequent report described the food reintroduction process of this cohort [33]. In line with previous literature, milk (74%), wheat (26%) and egg (17%) were the most offending food allergens. In contrast to previous reports 72% of the patients were allergic to only one instead of multiple foods and reintroduction of seafood showed no clinical or histologic disturbance at all [33].

In a large paediatric cohort (n = 319) Spergel et al. retrospectively compared the effectiveness of test-directed elimination diets to SFED and other empiric elimination variations [34]. Both diets accomplished histological response rates of 52%. Besides identifying the well-known food triggers, they found that EoE patients also reacted to meat (beef or chicken). The combination of the SFED with removal of meat increased their response rate to 77%. Furthermore tree nuts, peanuts and seafood were only rarely associated with EoE. This study has revealed further insights into responsible foods in EoE, but its retrospective character and the significant differences between groups make it less suitable for comparing the two dietary approaches.

Gonsalvez et al. were the first to describe the efficacy of SFED in a large group of adult EoE patients (n = 50) [35]. After six weeks 35 out of 50 (70%) patients had a peak eosinophil count of less than 10/hpf, and 47 (94%) patient's experienced clinical remission. Structured food reintroduction in 20 patients resulted in recurrence of pre-treatment peak eosinophil values from 2 to 61/hpf, whereby wheat (60%) and milk (50%) were most potential triggers of disease recurrence. These findings are in line with the most common offending foods in paediatric cohorts. At baseline, additional skin prick tests for food and aeroallergens were performed. In only 13% positive test results were predictive for responsible allergens. These results were confirmed by smaller series (n = 9) where they additionally analysed potential predictors of dietary response, however no significant differences in baseline characteristics were found between responders (n = 5) and non-responders [36].

Comparative results were subsequently obtained in a Spanish prospective study [31]. Lucendo et al. extended the SFED with rice and corn based on a pilot study, as food patterns differ in Spain compared to the USA and so do sensitizations patterns [37]. Similar to IgE-mediated intestinal food allergies, the most frequently consumed foods might be the most common trigger for EoE [38]. This new, region specific, SFED demonstrated histologic improvement in 73% of the adult EoE patients. The non-responders did not show any improvement at all, and no difference between groups was seen in means of demographic characteristics or allergy test results. This report also evaluated the maintenance of remission after dietary avoidance of the identified food allergens. From the 15 patients who fulfilled this avoidance diet for two years, all remained in clinical and histological remission. Despite the fact that they tailored their diet to demographic differences of food consumption, the same most frequent triggers were identified (wheat 60% and milk 50%) and result were comparable.

The first comparative prospective study between a food-specific serum IgE-targeted elimination diet (slgE-ED) and SFED found slightly higher response rates in slgE-ED group, although differences were not significant (73% (n = 26) vs 53% (n = 17), $p = 0.17$) [39]. It is remarkable that the remission percentage of SFED (53%) in this study is lower than formerly reported results. The disappointing response rates obtained with SFED might have been caused by selection bias since only patients with a positive IgE test followed a 6-week slgE-tailored diet, whereas non-IgE-sensitized patients completed a 6-week SFED. Furthermore, the small sample size, and the non-randomized classification of patients could have led to aberrant results.

Eventually, to restrict the high number of endoscopies, a new empiric elimination diet was developed: the four food elimination diet (FFED). This diet mainly focused on the four most common

food triggers for EoE in the Spanish diet (milk, wheat, egg and legumes). All 52 included patients followed a 6-week FFED, of whom 28 (54%) patients accomplished histological remission. Besides the four food groups also foods causing oral allergy syndrome were eliminated. Further research should validate this new, less intense dietary approach.

Discussion empiric elimination diets

Empiric elimination diets demonstrate modest to good response rates and are more tolerable than elemental diets. In contrary to other dietary research in EoE, direct comparison between SFEDs is possible since study designs are highly comparable and the same response rate endpoints are used. The first systematic review about dietary treatment, estimated an overall success rate of 71% [29].

Based on all reviewed reports, milk and wheat followed by eggs and soy are the major food triggers, whereas seafood and nuts play a minor role [29]. This is in line with the theory that the most commonly consumed foods are most likely to trigger an allergic reaction. Dietary habits vary within geographical regions [38]. If the efficacy of empiric dietary treatment can be improved by a more region specific diet, based on local dietary habits and consumptions, is still under debate. Since only studies from Spain and the USA are available, it remains the question whether the SFED with similar foods is also effective in other regions.

Besides, the possibility that responsible allergens are not excluded, lack of response can also be caused by non-compliance or cross-contamination, since product labels of food can be imprecise. The success of SFED depends on a strict elimination of the six foods, since little allergens may be enough to provoke the inflammation [28]. On the other hand, threshold levels for allergens may be higher due to the non-IgE mediated mechanisms.

The identification of the role of food allergy in EoE might be complicated through the influence of aeroallergens. Van Rhijn et al. showed that EoE patients tend to have polysensitization to both food and aeroallergens [40]. A variety of plant proteins cross-react with aeroallergens such as birch and ragweed pollens. EoE patients sensitized to birch pollen might experience a disease up-flare during pollen season, which may explain ineffectiveness of SFED.

Nevertheless the available data suggest that SFED is a feasible and effective dietary option for many EoE patients. With appropriate dietary counselling the diet can be effectively implemented in daily life because it allows the intake of a variety of staple foods including meats, fruits and vegetables. However, the food reintroduction process after SFED is time consuming and multiple endoscopies are required.

Test-directed elemental diets

Most empiric elimination diets are very extensive, particularly given that they are intended for long-term use and that many foods may be eliminated while only a few are responsible for the allergic inflammation. This notion stimulated the search for more specific tests to identify the causative allergens. If cutaneous or serum testing would reflect the EoE triggering allergen, a more patient-friendly and individually tailored diet could be compiled based on sensitisation pattern. As previously stated, patients with EoE often have atopic comorbidity and 15–43% of EoE patients present with concurrent food allergies [41,42]. However, it is questionable whether there is a direct link between IgE-mediated food allergy and the activity of the disease. The pathogenesis of EoE is complex; since its initial descriptions it has been associated with an IgE-mediated immune response. This theory was partly based on high prevalence of elevated serum IgE-levels and the eosinophil and mast cell dependent oesophageal inflammation. Additionally, both as for EoE as for some immediate-type food allergies, milk and eggs are the most common food triggers [43,41,16]. However, recent data showed that IgE-deficient mice were still able to develop an inflammatory pattern with similarities to EoE and anti-IgE treatment appeared ineffective in adult EoE patients [44–46]. These findings are sustained by positive dietary effects in non-sensitized patients. Therefore, it is very well possible that EoE pathophysiology is also partly cell-mediated and at least not exclusively IgE-mediated [11]. These ambiguities make it difficult to elect the most accurate allergy tests.

In immediate-type food allergy, food-specific IgE can be recognized by skin prick testing (SPT) and serum IgE testing [47,40]. SPT is a sensitive and widely accepted test for the detection of IgE-mediated

diseases [48]. This test detects hypersensitivity via allergen-specific IgE, bound to mast cells. A promising new variation of IgE testing, is allergen microarray ImmunoCAP, which is an in vitro serum IgE test for the assessment of specific IgE-antibodies against multiple allergens [40].

The atopy patch test (APT) is an allergy test which is used to record the presence of non-IgE (cell-mediated) delayed food reactions, which assesses the skin reaction to fresh food or commercial food extracts applied to a patients back for 48–72 hours [6,38]. In order to increase the chances of identifying the EoE causing allergen, most studies used a combination IgE and non-IgE specified allergy tests.

In 2002 Spergel et al. combined SPT and APT to tailor a diet for 24 paediatric EoE patients [6]. Milk and egg (both 36%) were the most common positive foods with SPTs whereas wheat (36%) was most commonly identified with APTs. Patients were positive to an average of 2.7 ± 3.3 foods (range; 0–13 foods). In a six-week diet all positive foods were avoided. If multiple positive foods had been identified and the diet posed nutritional risk, patients were placed on elemental diet. Symptomatic response was seen in 69% of the EoE patients and 75% of the patients showed histological remission. Peak eosinophil count decreased from 55.8 eos/hpf to 8.4 eos/hpf. This study has been criticized for concomitant corticosteroid treatment for other atopic diseases, additional use of elemental feeding, and lack of standardization in patch testing. Nevertheless these moderate response rates on a dual approach (APT&SPT) suggest a role for IgE-mediated and cell-mediated allergic mechanism.

Based on these results, the same group published a larger retrospective study, in which 146 children eliminated the foods that produced positive reactions by SPT and/or APT [42]. Besides the standard allergic food panel, patients were also tested based on their clinical history. Patients with a high number of positive foods or a poor adherence also required elemental diet ($n = 40$). Additionally, from 21 patients the food reintroduction process was analysed. In total 106 patients were solely treated with a test-directed diet, from which 72 (68%) patients completely responded and 19 (18%) patients partly responded. In accordance with previous reports egg, milk, and soy were most commonly tested positive with SPTs, while APTs were most frequently positive for wheat, corn and soy. Interestingly, foods rarely produced positive results on both test. More extensive patch test reactions were more likely to identify a causative food. However conclusions were drawn from a retrospective view, based on response rates without excluding the 40 patients treated with elemental diet.

Six years later this group continued their search for the optimal allergy test in EoE. Based on a retrospective analysis ($n = 319$) they determined predictive values for APT and SPT in identifying food triggers [34]. Combining APTs and SPTs, negative predictive values (NPV) were more than 90% for most foods except for milk (44%). Positive predictive values (PPV) were considerably more variable, ranging from 26% to 96%, with an average of 44%. It is remarkable that testing was done in sequences; if a patient had a positive SPT to a specific food, APT for that food was not performed. The test-directed diet (SPTs/APTs) in this report showed a response rate of 53%. Because of the poor predictive values for milk, the most common causative allergen for EoE, the issue remains whether allergy testing can be used as guidance for dietary treatment. Furthermore the amount of false-negatives and false-positives was substantial.

Henderson et al. reported similar response rates and predictive values. In a retrospective trial 15 out of 23 (65%) patients were histological in remission after a test-directed diet. NPVs were calculated by using SPT results only, and foods were reintroduced empirically instead of by using a test-directed strategy. Therefore the NPVs for wheat (63%), egg (60%) and milk (35%) were not reliable [26].

The first prospective study among paediatric EoE patients observed a slightly lower response rate of 45% ($n = 12$) after avoidance of two food groups: milk/beef and eggs/chicken [49]. The authors concluded that their study might have been useful in the diagnostic pathway but identifying the triggering antigen was unsuccessful. They even suggested that elemental diet should be the first choice in dietary treatment.

The effectiveness of test-directed diets is even lower in adult series, although data are scarce. In the first adult study, six patients were kept on an elimination diet, avoiding wheat and rye for six weeks. Patients sensitized to grass pollen, wheat and rye but not to food allergens (e.g., eggs, milk, and fish) were included. This test-directed diet based on SPTs and IgE-testing was unsuccessful in reducing disease activity, based on clinical evaluation [50].

A study by Molina et al. prospectively analysed the efficacy of a six-week elimination diet based on SPTs and ATPs testing to 26 fresh and commercial food extracts. In contrary to previous reports the most common food sensitizations patterns in the 15 included patients were legumes, barley, rye, tomato and fruits (all 36%). Unfortunately only four (26%) patients achieved complete remission [51].

Most recent published data of a retrospective study showed histological remission in 32% of the 22 included EoE patients, after a test tailored diet (SPTs and APTs). These results are in agreement with previously reported suboptimal response rates in adults [36].

To improve the low efficacy of SPT and APT directed diets, van Rhijn et al. composed a diet based on sensitization patterns identified by a microarray component-resolved diagnosis (CRD) test, a technique by which sensitization to an allergen component can be investigated instead of sensitization to the entire allergen (ImmunoCAP ISAC, Phadia). This technique claims to have a higher sensitivity and gives more insight into cross sensitizations. Unfortunately this new approach was not effective, with response rates below 10% ($n = 15$) [52]. Due to disappointing results this prospective study was prematurely terminated after the inclusion of 15 patients [53]. Possible explanations for the low success rate are that the food allergies in EoE are not serum IgE mediated or that the responsible allergens were not present in the array.

Consequently the first systematic review on dietary treatment in EoE estimated an overall efficacy of less than 50% in 626 patients (594 children) treated with test-directed diets. Skin prick test and food-specific IgE measurements were neither sensitive nor specific for identifying EoE triggers [29,38,54].

Discussion test-directed elimination diets

A test-directed diet could be the ideal solution for EoE, since it allows elimination of only the causative foods and potentially results in an acceptable lifelong diet. However the ideal test has not been developed yet. The utility of positive allergy tests for guiding an individual elimination diet is extremely doubtful due to several factors.

First of all, SPTs may not be able to identify the right allergen since EoE might be provoked by a combination of IgE and cell-mediated immune response. Second, APTs, specified for this cell-mediated allergy testing, have not been well standardized and interpretation of results is difficult [41]. The heterogeneity of allergy test used in studies makes it difficult to compare response rates and predictive values. This diversity could have contributed to the observed substantial variability of positive and negative predictive values. Furthermore, as in food allergy in general, the high false-negative and false-positive test results decrease the clinical relevance of positive test results. Cross-reactivity or concurrent IgE-mediated diseases could influence the food-specific IgE test results. Interpretation of positive results is also challenging since there are no clear data on the amount of allergens necessary to elicit an immune response [44].

Another explanation could be that test-directed elimination diets are ineffective because cutaneous or serum tests might not be indicative of local oesophageal sensitizations. Previous research demonstrated local B-cell and IgE production in the oesophageal mucosa [55]. This might imply that the oesophageal mucosa is immunologically active tissue which can induce a local immune response. Serum IgE testing might not detect this local IgE production as perhaps it never reaches the serum [56]. In addition, systemic inflammatory biomarkers as C-reactive protein or leukocytes are rarely elevated in EoE [57]. Further research is warranted to clarify these local oesophageal reactions.

In conclusion, current allergy tests are of limited value in confirmation of the diagnosis and identification of the causative allergen.

Conclusion

There are several therapeutic options available for EoE patients, however all methods have their own disadvantages. Dietary treatment could be an attractive alternative for many patients, but the current approach is far from perfect as it may have a severe impact on quality of life, it is expensive and has a poor taste (amino acid-based diet), or it is just not very effective (test based elimination diets). Whether or not a dietary treatment would be suitable for individual patients depends on the personal needs of each patient and the experience of the medical team.

Elemental diet is most effective in achieving disease remission and mucosal healing although these successes are undermined by multiple disadvantages. Patient's adherence is diminished by its: (1) low palatability, (2) major lifestyle modifications with social limitations, (3) high cost which are not always covered by insurance and (4) long way to subsequently identify the causative allergens. Nevertheless the extremely high overall response rates might outweigh the drawbacks, particularly if the taste of the product can be improved.

The **SFED elimination diet** attempted to overcome the limitations of other diets, by the eliminating only the most commonly allergy associated foods (milk, soy, eggs, wheat, peanuts, and seafood). Response rates are moderate, but patients adherence improved with this less intensive approach [29]. Most identified triggers were wheat and milk, regardless of age or geographical region [58,25]. The use of endoscopy after each step in the food reintroduction process makes this approach very invasive.

Test-directed elimination diets use allergy test to identify EoE triggers. However, low response rates, great heterogeneity between studies and low reproducibility questions the usefulness of this approach. Concurrent atopic diseases can influence allergy test results and neither negative nor positive predictive values for allergy tests were valuable [47]. It thus seems a more sensitive test is required for this approach.

Several limitations hinder interpretation of previous reports. First of all there are no randomized or placebo controlled trials available on dietary treatment for EoE. Secondly, there is great variation among study designs, clinical and histologic response is not uniformly determined, and endpoints for EoE therapy differ. Furthermore, most of the studies are retrospective and sample sizes are small, thereby are most results based on paediatric cohorts. Additionally, there might be geographical differences in most common EoE triggers since local dietary habits influence sensitization patterns. A more region adjusted diet might improve the efficacy of dietary treatment.

Our conclusion is therefore that dietary treatments for EoE seem highly promising, but further refinement and new diagnostics are required before it can become standard care.

Practice points

- Food and aeroallergens are believed to play a major role in the pathogenesis of EoE
- Dietary therapy with elimination of causative allergens is often used in EoE
- The main modes of dietary treatment are elemental diets and empiric- or allergy test-directed elimination diets
- Elemental diet is most effective but poor taste makes adherence challenging
- Dietary treatments for EoE seem promising, but further refinement is required before it can become standard care

Research agenda

- Prospective studies are necessary to define appropriate efficacy rates of dietary treatment
- The development of less invasive disease monitoring markers can facilitate dietary treatment
- Long-term efficacy of dietary treatment in EoE should be evaluated

Conflict of interest

AB received research funding from AstraZeneca, Nutricia, Endostim, MMS, and Shire, and received speaker fees from MMS, AstraZeneca and Shire.

Statement of contribution

MjW: conception and design of the study; drafting the article; final approval of the version to be published.

BV: revising the article critically for important intellectual content; final approval of the version to be published.

AB: revising the article critically for important intellectual content; final approval of the version to be published.

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