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Dietary therapies for eosinophilic esophagitis

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Eosinophilic esophagitis (EoE) represents a prevalent chronic esophageal disorder. Since the condition was first described, its pathophysiology has been known to have an immuneallergic origin, but the high response rate to dietary therapies based on feeding patients exclusively with amino acid-based elemental formulas (with complete elimination of table foods) has clearly established EoE as a particular form of food allergy. Nevertheless, the management of EoE in clinical practice remains widely heterogeneous, with topical steroids being a therapeutic mainstay. However, a growing body of evidence points to dietary therapy as an effective treatment option for both children and adults with EoE, as this approach is capable of achieving a sustained symptomatic and histological response without resorting to drugs. This article reviews the available data on the major types of dietary therapy for EoE, including elemental formula diets, skin allergy testing-directed elimination diets and empirical elimination diets based on common food allergens.

Keywords: diet • diet therapy • eosinophilic esophagitis • food hypersensitivity • food reintroduction • treatment

Eosinophilic esophagitis (EoE) is an immunoallergic mediated disease characterized by significant eosinophilic infiltration into the esophageal mucosa, chronic or recurrent esophageal symptoms, and failure to respond to proton pump inhibitors (PPI) therapy [1]. EoE persists from childhood into adulthood [2], significantly impairing the quality of life of patients suffering from this disorder [3,4]. EoE constitutes a common cause of chronic esophageal symptoms that is increasingly prevalent in both Europe [5,6] and the USA [7,8], where EoE is found in approximately 43-52 cases per 100,000 inhabitants. In spite of having first been described as a distinctive clinicopathological syndrome only 20 years ago [9,10], knowledge of the epidemiology, pathophysiology and natural history of EoE has increased exponentially. In spite of this, the clinical management of EoE remains controversial, with treatment methods varying widely [11]. Not only are there differences in the management of the disease with regard to patient age (children vs adults) [12], but also depending on the facilities available [11]. Topical swallowed corticosteroids, including fluticasione propionate [13-15], and budesonide [16,17], remain the most commonly used therapeutic option for EoE in both children and adults [11]. esophageal inflammation Symptoms and

effectively usually remit for the duration of treatment, but recurrence of the disease after drug withdrawal is the standard, calling for repeated cycles or even chronic administration. Steroid-sparing drugs such as comoglicate [18] and montelukast [19], which are useful in other atopic disorders, are so ineffective against EoE that their use is not recommended [1]. Biological therapies based on monoclonal antibodies have either proven wholly ineffective against EoE, as in the case of infliximab [20] (anti-TNF-alpha) or omalizumab [21] (anti-IgE), or only produce a partial reduction of eosinophilic inflammation with no significant clinical effect, as is the case for the anti-IL-5 drugs mepolizumab [22,23] and reslizumab [24]. Endoscopic dilation for treating especially adults patients has been demonstrated to improve the symptoms in the majority of cases, at least in the short-term [25]. It has no effect on the underlying inflammation [26], so patients usually have to undergo repeated procedures.

Since the first reports of the disease in children, the efficacy of dietary modifications in inducing the remission of EoE has been well known [27]. Because of the limitations of therapeutic modalities based on drugs or repeated mechanical procedures in treating EoE, interest in this drug-free alternative has been renewed. An increasing amount of research reported

Table 1. Major studies assessing the efficacy of exclusive feeding with an amino acid-based elemental diet in eosinophilic esophagitis patients.

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Study (year)	Design	Age	Main outcomes	Ref.
Kelly <i>et al</i> . (1995)	Prospective	Children	8/10 patients: complete resolution of symptoms; 2/10: symptom improvement. 100%: normalized esophageal histology	[27]
Markowitz et al. (2003)	Prospective	Children	49/51: symptom improvement, all with normalized esophageal histology	[28]
Liacouras <i>et al</i> . (2005)	Retrospective	Children	160/164: histological restoration	[18]
Kagalwalla <i>et al.</i> (2006)	Retrospective	Children	22/25: complete histological remission (<10 eos/hpf) + 2/25: partial histological response (11–20 eos/hpf)	[29]
Kagalwalla <i>et al</i> . (2012)	Retrospective	Children	10/12: histological restoration	[30]
Henderson <i>et al</i> . (2012)	Retrospective	Children	47/49: histological response	[31]
Spergel <i>et al</i> . (2012)	Retrospective	Children	Histological remission rate of 95%	[32]
Peterson <i>et al.</i> (2013)	Prospective	Adults	13/18: complete histological remission; 4/18: > 50% reduction of baseline peak eosinophil count	[33]

Histological response is defined by a peak eosinophil count <15 eos/hpf after dietary intervention.

eos/hpf: Eosinophils per high power field.

over the past few years has led specialists to consider dietary therapy as the preferred therapeutic option for treating EoE because it seems to produce the most prolonged response. Different dietary approaches are available for EoE, including elemental diets, allergy testing-directed elimination and empirical elimination diets. All of them have been used in adult and pediatric EoE patients with various results, as starting points for control, with the expectation that reintroduction of foods will be undertaken to ultimately determine the diet that is least restrictive for each individual patient. This review aims to assess all available published evidence supporting exclusive dietary treatment for EoE patients in terms of efficacy in inducing disease remission, feasibility and long-term effects.

Elemental diets

Elemental diets are synthetic dietary formulations that lack any antigenic capacity since all proteins have been eliminated. The nitrogen source is exclusively provided by single amino acids, while carbohydrates, fats and micronutrients are formulated to provide complete nutritional needs.

Initial uses of elemental diets in EoE

The first evidence of the efficacy of dietary interventions for treating EoE was published back in 1995, when Kelly *et al.* used an amino acid-based elemental formula for exclusively feeding 10 children with intense esophageal eosinophilia attributed to reflux disease and which was refractory to medical or surgical treatment [27]. Eight patients showed total resolution with the other two exhibiting improvement of symptoms in parallel with an average reduction of eosinophil peak counts from 41 eos/high power field (hpf) to 0.5 eos/hpf after 8 weeks of treatment. A subsequent prospective study also carried out in children by Markowitkz *et al.* in 1998 confirmed these findings [28] by demonstrating that 49 out of the 51 recruited patients fed with an elemental diet presented improved

symptoms and reduced eosinophilic infiltration (from 33.7 eos/hpf to 1 eos/hpf).

Effectiveness of elemental diets in children with EoE

Several retrospective studies have further corroborated the evidence for the high efficacy of elemental diets observed in this initial research on children; thus, Liacouras *et al.* demonstrated an overall efficacy of 97.5% (160/164 patients) [18] while two retrospective studies conducted by Kagalwalla *et al.* showed an efficacy of 88% (22/25) [29] and 83% (10/12) [30], respectively. All three studies showed infiltration reductions down to less than 10 eos/hpf. A recent retrospective study by Henderson *et al.* also demonstrated EoE resolution in 96% (47/49) of the children recruited, with a reduction from a mean of 51 to 1 eos/hpf [31]. These results are identical to the 95% resolution reported by Spergel *et al.* [32].

Elemental diets in adult EoE

The positive, extensively documented good results obtained in children have recently been corroborated in adults. Peterson et al. prospectively recruited 29 adult EoE patients and fed them an elemental diet for 4 weeks. Of the 18 patients who fulfilled the study protocol, 13 achieved a complete histological response (<10 eos/hpf) and 4 additional patients showed an eosinophil peak reduction of over 50% with regard to baseline levels [33]. In addition to the results of the studies described earlier, several other case reports and case series have also corroborated the finding that feeding EoE patients solely with an elemental diet effectively induces remission of the disease [34-39]. In summary, despite the absence of randomized controlled trials (RCT) and with most of the data coming from pediatric series, observational studies provide strong evidence for the overall efficacy (in 90% of cases) of elemental diets in inducing histological remission of EOE (TABLE 1). This seems to be accompanied by improvement or resolution of symptoms in almost every patient. These results

show that elemental diets seem to be at least as effective as topical steroids in inducing EoE remission, although comparative studies have not been developed to date.

Disadvantages & limitations of elemental diets in EoE

The absence of drug-related side effects must be balanced with the numerous drawbacks of this type of dietary intervention in which consumption of all table food must be avoided. The most important disadvantages are its unsavory taste, for which up to 80% of patients (in some series) must be fed through a nasogastric tube [18], its high cost and its unfeasibility for longterm use, especially in older children and adults, in whom the prohibition of all solid food leads to a poor treatment adherence rate. Additionally, it should be considered that young children who do not have the need to chew do not promote facial muscle development and may promote delayed/poor speech, so if needed, elemental diet should be planned for a limited time and followed by a food reintroduction challenge.

Skin allergy testing-directed elimination diets *Rationale for seeking new dietary approaches*

In spite of the good results obtained with elemental diets in achieving drug-free remission of EoE, the adherence to this kind of diet for long periods of time is complicated and unsuited to older children and adults from a nutritional perspective. It is for this reason that alternative dietary interventions have been elaborated, principally through the identification of specific food triggers for EoE. The thinking behind this methodology is that specific exclusion of these foods from the diet should produce comparable results, but in a more comfortable and feasible fashion for patients, who would be able to follow a near-normal diet and avoid a deterioration in their health-related quality of life.

Skin allergy testing-directed food exclusion in pediatric EoE

The use of allergy testing-directed food exclusion to treat EoE was first described by Spergel et al. in 2002 [40]. These authors identified potential food triggers for EoE by using a combination of skin prick tests (SPTs) and atopy patch tests (APTs); patients were subsequently advised to avoid eating those foods, which gave a positive result. After excluding an average of 5 foods from the diets of the 24 children recruited to the study, the authors observed histopathological remission of EoE in 18 of them (77%). Among these subjects, the mean peak eosinophil count decreased from 55.8 to 8.4 eos/hpf, accompanied by an improvement in symptoms in all cases. These preliminary results have been updated in subsequent studies by the same group [41,42], with the latest being published in 2012 [3]. This last paper retrospectively documents that 53% of patients who followed an allergy testing (SPT and APT)-directed exclusion diet achieved complete resolution of the disease, a result similar to that published in 2005, in which, after excluding patients being managed with an elemental diet, only 49% (72/146) of the children participating in the study achieved EoE remission after excluding foods

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identified with the aid of allergy testing results. Unfortunately, the initial 77% efficiency rate observed in the Spergel *et al.*'s initial study [40] has never been reproduced. The actual efficacy of skin allergy testing-directed exclusion diets thus remains controversial, especially regarding the methodology for carrying out and reading APT results [43].

Despite the fact that the diagnostic accuracy of skin-prick testing is insufficient for the development of dietary regimens for EoE patients as stipulated by food allergy management guidelines [44], an overall efficacy of around 50% for food elimination diets based solely on these results has been observed in recent studies published by various research groups. Thus, Henderson et al. documented EoE remission in 65% (15/23) of children who followed an allergy testing-directed elimination diet, as manifested by a drop in mean peak eosinophil count from 38 to 7 eos/hpf [31]. Similarly, Kagalwalla et al. achieved remission of EoE in 63% (52/82) of patients after following the same dietary strategy [30]. Nevertheless, other studies have found significantly lower remission rates. For example, Liacouras et al. documented disease remission in only 24% (18/75) of pediatric EoE patients [18]. Other researchers have observed only a partial histopathological response, with eosinophil peak counts persisting over 15/hpf after the restriction of foods with positive allergy test results in 40% of children participating in the study conducted by Al-Hussaini et al. [36] and in 45% of the 11 children studied by Rizo Pascual et al. [39].

Skin allergy testing-based food elimination in adult EoE

As is the case with elemental diets, studies on the utility of skin allergy testing-directed elimination diets in adult EoE patients are scarce. The best documented research to date has been conducted by Molina-Infante *et al.*, who excluded every food which gave a positive result after SPT, prick–prick test (PPT), and ATP, documenting disease remission in only 4 out of the 15 study subjects (24%) [45]. A second study performed with adults observed symptomatic improvement in only one of the six EoE patients studied, with no histological remission [46].

Limitations of skin allergy testing in identifying EoE food triggers

The wide variability in the efficacy of food elimination diets based on the results of allergy testing as reported in the aforementioned studies as well as in other case reports and short caseseries [38,47,48] has only served to stoke the debate over the exact immunopathological mechanism underlying the eosinophilicpredominant inflammatory response that characterizes EoE. A growing body of evidence points to a cell-mediated delayed reaction against certain foods in the pathophysiology of the disease rather than an IgE-mediated reaction [49]. It is probably for this reason that IgE-based allergy tests failed to identify the exact food triggers in a majority of patients in several pediatric [50-52] and adult series [33,45,46,48,53]. In fact, food-specific IgE serum measurements and SPTs have proven to be neither sensitive nor specific methods for retrospectively predicting EoE triggers in

Table 2. Major available studies assessing the efficacy of skin allergy testing-directed elimination diets in the treatment of eosinophilic esophagitis.

Study (year)	Design	Age	Main outcomes (histological response rate)	Ref.
Spergel <i>et al.</i> (2002)	Prospective	Children	77% (18/24)	[40]
Spergel <i>et al.</i> (2012)	Prospective	Children	53%	[32]
Henderson <i>et al.</i> (2012)	Retrospective	Children	65% (15/23)	[31]
Kagalwalla <i>et al.</i> (2012)	Retrospective	Children	63% (52/82)	[30]
Al-Husani <i>et al.</i> (2013)	Prospective	Children	40% (4/10)	[36]
Pascual <i>et al.</i> (2011)	Prospective	Children	45% (5/11)	[39]
Liacouras <i>et al.</i> (2005)	Retrospective	Children	24% (18/75)	[18]
Molina- Infante <i>et al</i> . (2012)	Prospective	Adults	26% (4/15)	[45]
Simon <i>et al. (2006)</i>	Prospective	Adults	0% (0/6); 1/6 patients with symptom improvement	[46]

Histological response is defined by a peak eosinophil count <15 eos/hpf after dietary intervention.

eos/hpf: Eosinophils per high power field.

adult patients [53,54]. This is due to the fact that even though EoE generally occurs together with other IgE-mediated atopic diseases in a single patient, each condition has a different underlying mechanism. As a result, the clinical utility of IgE testing for dietary intervention in patients with EoE remains limited. According to the latest international consensus document for managing EoE [1], neither positive SPT, serum IgE, nor ATP results should be used alone to diagnose food triggers in EoE patients, which means that food restrictions should not be recommended if based exclusively on a positive test result. At the present time, food triggers can only be identified by first documenting disease remission after specific food antigen avoidance, followed by EoE recrudescence upon specific food reintroduction. This is the strategy followed by empirical elimination diets and food reintroduction protocols, which will be discussed below.

In summary, a wide variability has been observed in the response rate to skin allergy testing-directed food elimination in EoE patients (ranging from 26 to 77%) in the available series, most of which have involved pediatric EoE cases. Still, the

overall response rate does not seem to be above 50% in terms of histological disease remission (TABLE 2).

Empirical elimination diets

Rationale & effectiveness in pediatric EoE

Because of the low sensitivity and specificity of allergy test results in identifying EoE food triggers, the limited capacity of skin allergy testing-directed food elimination in inducing disease remission, and the disadvantages of elemental diets, a new approach in the management of EoE patients was assessed by Kagalwalla et al. in 2006. The new dietary approach consisted of eliminating several, but not all, intact food proteins with a six-food elimination diet (SFED) [29]. The authors specifically excluded those foods most commonly associated with food allergies in children, which were also those most commonly reported to cause esophageal mucosal injury in pediatric EoE. The six foods included milk protein, soy, egg, wheat, peanut/ tree nuts and seafood. In the initial report on the efficacy of this SFED, 26 out of 35 treated children (74%) achieved complete histological remission (<10 eos/hpf), with a partial remission (11-20 eos/hpf) being documented in 3 more children after a 6-week period. These results have recently been corroborated in a new retrospective study in which the classic SFED was extended to include foods which gave a positive result in allergy tests [31]. Eighty-one percent of the participating children (21/26) achieved histological remission, with a drop in the average peak eosinophil count from 76.5 to 2.5 eos/hpf.

Empiric elimination diet in adult patients

Similar results have been obtained in adults. Thus, Gonsalvez *et al.* documented a 70% remission rate among 50 adult EoE patients prospectively recruited from the same area studied by Kagawalla in the original report who followed an SFED that also included foods, which had given a positive result in a skin allergy test [53]. The only study conducted in Europe using an empirical SFED approach was that published by Lucendo *et al.* The response rate was 73% (49/67 patients) [54], with a reduction in peak eosinophil counts from 47.9 to 3.5 eos/ hpf and a significant improvement in symptoms in every responding patient. In this study, the "classic" SFED was expanded to include common food allergens in this particular population (legumes, rice and corn).

In conclusion, although studies using empirical SFED are still limited, they show a fairly uniform agreement in the observed remission rates, which are all around 75% (TABLE 3), independent of the age of the study subjects. The absence of variability compared to skin allergy testing-directed food elimination, along with the improved compliance over elemental diets, makes the SFED and its variants a feasible initial approach in the dietary management of EoE.

Additional dietary strategies

Alternative dietary interventions have occasionally been used for the management of EoE patients, with the two most commonly cited restrictions being cow's milk avoidance and a gluten-free diet (GFD). After having identified cow's milk as the most common EoE trigger, Kagalwalla *et al.* used cow's milk elimination alone to treat a series of pediatric EoE patients [30]. The authors observed histological remission of the disease in 11 out of 17 treated children (65%), and symptom improvement or resolution in all of them. A younger age and lower eosinophil peak count at baseline conditions were both significantly associated with increased response rates. However, the surprisingly high efficacy of this strategy may have been influenced in this study by the inclusion of patients with a particular allergy background, that is, a previous IgE-mediated cow's milk allergy for which the patient was undergoing desensitization. Indeed, an increasing number of studies has documented the development of EoE after oral immunotherapy with milk [55] or egg [56].

The relationship between EoE and celiac disease (CD) remains unclear; while an increased prevalence of CD has been documented among pediatric EoE patients [57], an increased frequency of the HLA-DQ2/DQ8 genotypes that predispose individuals to CD has not been observed in adult EoE patients [58]. The efficacy of GFDs has been assessed in several case reports and short case series based-studies with uneven results [36,47,59-61] regarding their histological effect on eosinophilic esophageal infiltration. Additional studies are needed to assess the true efficacy of these singlefood avoidance strategies in EoE and to clearly define their position in the therapeutic algorithm of the disease.

Identifying food triggers for EoE & sustained efficacy of dietary treatment

Every of the available dietary interventional strategies in EoE are aimed to induce disease remission, as an starting point for control the disease and its potential triggers, with the expectation in all patients that reintroduction of foods will be undertaken to ultimately determine the least restrictive maintenance diet for each individual patient. In fact, several studies have determined the main food triggers for EoE by means of sequential food reintroduction after disease remission has been achieved through successful dietary treatment [53,54,62]. Consumption of an excluded food after disease remission constitutes a food allergy challenge; the use of endoscopies and biopsies to document any type of disease recrudescence after challenge allows specialists to pinpoint, which food or foods actually trigger the disease so that they can be excluded from the diet indefinitely. The results of this method are consistent in all studies published to date, with milk and wheat being the major food triggers for EoE in nearly 50% of cases and with no differences between children and adults or across different geographical areas. Differences in the prevalence of other food triggers have, however, been documented between American and European studies, raising the question of whether empirical elimination diets should be tailored to take the staple diets and allergy sensitization patterns of each geographical study area into account. The number of foods triggering EoE has also been demonstrated to vary among the different studies, being one single food in most of north-western American (pediatric and adult) patients [53,62], but two or more in most of Spanish adults with EoE [54]. Even when very limited information is

Table 3. Available published studies assessing the effacy of empirical six-food elimination diets (and variants) for the treatment of eosinophilic esophagitis.

Study (year)	Design	Population	Main outcome (histological response rate)	Ref.
Kagalwalla <i>et al.</i> (2006)	Prospective	Children	74% (26/35); 3/35 additional patients exhibited a partial response (11–20 eos/hpf)	[29]
Henderson <i>et al.</i> (2012)	Prospective	Children	81% (21/26)	[31]
Gonsalves <i>et al.</i> (2012)	Retrospective	Adults	70% (37/50)	[53]
Lucendo <i>et al.</i> (2013)	Prospective	Adults	73% (49/67)	[54]

Histological response is defined by a peak eosinophil count <15 eos/hpf after dietary intervention.

eos/hpf: Eosinophils per high power field.

available on this topic, a more varied diet (such as the Mediterranean diet compared with the north-western American one, or the adult compared with the children diet), could increase the probability of developing a food allergy manifested as EoE.

The two studies that provided specific data regarding the longterm efficacy of prolonged exclusion of identified food triggers have been developed on adult patients: In the first one (which is published as an abstract) no disease recurrence was demonstrated after one year of dietary maintenance among the nine recruited patients [63]. In the second, disease remission was maintained for up to 3 years in every patient who adhered to the diet [54]. With regard to the possibility of inducing tolerance to foods found to trigger EoE after prolonged abstinence from these items, the few studies that have been carried out are disappointing [62] since EoE universally reappeared after food reintroduction challenge, even after a remission period of up to 4 years.

Expert commentary

A growing body of evidence has justified dietary treatment as a prime strategy in the management of EoE in both children and adults. Even when limitations for each of the different proposed options exists (TABLE 4), the ability to achieve and maintain long-term, drug-free disease remission is currently feasible for many EoE patients. It is clear that histological remission – not merely improvement of symptoms – should be the principal goal of dietary treatment as this is what allows the subsequent identification of individual food allergens through sequential food reintroduction challenge.

From a practical point of view, elemental diets may be useful in treating younger children (in whom the avoidance of other

Table 4. Comparative advantages and drawbacks of the major available food treatment alternatives for eosinophilic esophagitis.

Advantages	Limitations		
Elemental diet			
Highest effectiveness	Unpleasant taste, table food must be avoided		
Fast response time	Often, gastric tube administration in children		
Easy instructions	High cost of elemental formula		
Minor risk of dietary contamination	Poor adhesion		
Allergy testing is not needed	Long-term supply		
	Long-term use in younger children may delay facial muscle development and speech.		
Skin allergy testing-directed elimination diet			
Ability to remove less food from patients' diets	High variability in response rates		
Exclusive removal of specific foods	Low sensitivity and specificity of allergy testing		
Rapid normalization of diets	Low standardization for atopy patch testing		
Moderate efficacy	Possible dietary contamination		
Empiric elimination diet (six-food elimination diet)			
Exclusive removal of the most common antigens	Possible dietary contamination		
Allergy testing is not needed	Lack of standardization of protocol		
Moderately high efficacy	The adequacy of diets to local customs should be assessed		
Rapid normalization of diet	Difficulties in reading/interpreting food labeling		

In addition to those presented in the table, all dietary interventions share the need for repeated endoscopic and bioptic assessment during food reintroduction challenge to identify specific food triggers as a common inconvenience; the possibility of a drug-free prolonged remission of the disease is a common advantage for all dietary treatment alternatives.

forms of table food in the medium term would be feasible), and also to bridge the gaps between each individual food reintroduction. Diets based on skin allergy test results offer the advantage of being less restrictive in the number of eliminated foods than other options, but the lack of standardized methods for conducting APTs means that it should only be implemented by experienced clinicians who have proven its efficacy. Taking all these considerations into account, empirical elimination diets based on food allergy sensitization patterns of each geographical study area are gaining a reputation for being a valid and highly effective alternative for many adult and pediatric patients.

The main disadvantages of dietary interventions derive from the need for repeated endoscopies, first to monitor treatment and then during the food reintroduction phase, which allows the exact identification of EoE triggers. The number of foods for reintroduction varies between 5 and 8, depending on the study protocol. Considering that once a specific food is identified as a cause of EoE it must be removed from the diet, probably indefinitely, it is advisable to perform histological testing after each food is reintroduced, as well as to establish an individualized reintroduction sequence for each patient in order to guarantee normalization of the diet as soon as possible. The willingness of patients to undergo repeated endoscopies improves if they are performed under sedation [64], which is mandatory in the case of children. The report of neurotrophic changes in neonatal rat brains after repeated propofol exposition [65,66] has recently motivated some safety concerns on their pediatric use, despite having been reported that repeated deep sedation with propofol was safe in very young children [67]. Research on this topic is scarce and the potential risks should be balanced.

Two distinct issues need to be urgently investigated in EoE: the identification of non-invasive markers of disease activity, which would eliminate the need for repeated endoscopies and biopsies in the evaluation of EoE patients, and the development of new sensitive and specific allergy tests that can predict the exact food triggers responsible for causing EoE in order to design exact exclusion diets. With regard to the former, no serum or fecal markers predicting the presence of inflammation in the esophagus have been identified to date, although a minimally invasive string test has shown promise in monitoring inflammatory activity in the esophageal mucosa [68]. The likelihood of developing more sensitive and specific allergy tests is even lower due to difficulties in assessing cell-mediated delayed hypersensitivity immune responses, along with the absence of a fully explanatory pathophysiological model for EoE.

Finally, it is interesting to note that the various dietary interventions available for EoE patients show relatively similar results with regard to efficacy, ranging from 96 to 70% [27-29,31,32,53,54]. We can thus safely assert that in most of patients suffering from EoE, the disease is triggered and maintained exclusively by food, with a very small remainder attributable to airborne allergens. The differences in the efficacy of elemental diets compared with empirical elimination diets can probably be attributed to allergies to those foods that are not restricted from the diet, usually fruits and vegetables. In fact, most adult EoE patients exhibit sensitization to crossreactive panallergenic components [69], including profilins and lipid transfer proteins (LPT), which are largely found in food of vegetable origin, and are thus very difficult to exclude definitively from a healthy, well-balanced human diet.

Five-year view

We anticipate a much greater use of diet as a first-line treatment for EoE in both children and adults in the coming years. This will be primarily determined by the simplification of treatment regimens with the development of empirical four-food exclusion diets (which exclude only the most likely food triggers in a given population), the adaptation of food exclusion schemes to consumption habits and patterns of allergic sensitization, and the effective replacement of definitively excluded foods by well tolerated and nutritionally adequate alternatives. An example of the latter is the recent demonstration of tolerance to a cow's milk-derived hydrolyzed formula in patients with EoE triggered by milk [70]. All of the aforementioned developments should contribute to reconciling prolonged remission of EoE with a feasible diet and an adequate quality of life.

The identification of new patterns of the disease within the common phenotype of EoE defined by a dense esophageal eosinophilic inflammation will allow for different dietary interventions to be matched to specific patient profiles; for example, the specific exclusion of a single food in patients with history of IgE-mediated allergy who underwent to an attempt of inducing tolerance for this particular food. Multicenter prospective studies involving patients from different geographic regions and which contemplate long-term maintenance and follow-up are needed to confirm the potential of dietary treatment as an efficient, drug-free and safe alternative for the management of EoE as evidenced by the latest available research.

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Key issues

- Dietary intervention has been demonstrated to be a therapeutic option for eosinophilic esophagitis (EoE), that seems to be almost equivalent to topical steroids in terms of achieving histopathological remission.
- After initial studies assessing the efficacy of dietary interventions in pediatric EoE patients, recent prospective studies in adults have also demonstrated that the response in terms of histological remission and symptom improvement rates are comparable to those previously reported in children.
- Preliminary results indicate that dietary therapy may offer a potential long-term remission of EoE without the risk of drug-related side effects.
- Exclusive feeding with an elemental formula is the most effective option for treating EoE, followed by an empirical six-food elimination diet. Because the results vary widely, the least effective option is the skin allergy testing-directed elimination diet, which limits this option to experienced clinicians and for use in children.
- Due to the disadvantages of elemental diets, in which all table food is restricted, and to the wide variability in the efficacy of skin allergy testing-directed diets, empirical six-food elimination diets (and their variants) will probably become the treatment of choice for most EoE cases in the near future.
- Further multicenter and trans-oceanic comparative studies are necessary to determine the true effectiveness of each dietary strategy. Emphasis should be placed on discovering new minimally or non-invasive markers of disease activity and accurate tests for detection of EoE food triggers in order to replace the repeated endoscopies needed in food reintroduction protocols.

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management of eosinophilic esophagitis (EoE) in children and adults incorporate the huge body of knowledge accumulated in the 20 years of history of EoE. As a reference document, it integrally revises and discuses all the available relevant information on EoE, including therapeutic management, and provides recommendation for further research.

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EoE patients retrospectively identified after reviewing pediatric esophageal biopsy specimens from up to 1999 were contacted 15 years later and answered questionnairebased study; quality of life was significantly decreased among patients compared with control subjects, while EoE symptoms persisted along the time. This article clearly establishes that pediatric EoE persists into adulthood in absence of treatment.

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