

# Dietary therapy for eosinophilic esophagitis



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Eosinophilic esophagitis is a chronic, immune-mediated esophageal disease triggered predominantly, but not exclusively, by food antigens. Presently, available food allergy tests are suboptimal to predict food triggers for eosinophilic esophagitis, especially in adults. Elemental diets (exclusive feeding with amino acid–based formulas) and empiric 6-food elimination diets (withdrawing milk, wheat, egg, soy, nuts, and fish/seafood for 6 weeks) have consistently shown the best efficacy rates. However, their high level of restriction and need for multiple endoscopies have hampered their implementation in clinical practice. Currently, milk, wheat/gluten, and egg are the most common food triggers in children and adults from the United States, Spain, and Australia. Hence less restrictive empiric schemes, such as a 4-food elimination diet (dairy, gluten-containing cereals, egg, and legumes) or a 2-food elimination diet (dairy and gluten-containing cereals) have been lately developed with good efficacy rates (2-food elimination diet, 43%; 4-food elimination diet in adults, 54%; and 4-food elimination diet in children, 64%). A step-up approach (2-4-6) might result in prompt recognition of a majority of responders with few food triggers, reducing the number of endoscopies and costs and shortening the diagnostic process. Standardization of food reintroduction, novel food allergy testing, and studies evaluating a milk elimination diet in children and the long-term outcomes of dietary interventions are warranted. (*J Allergy Clin Immunol* 2018;142:41-7.)

**Key words:** Eosinophilic esophagitis, diet, food allergy, milk, wheat, egg

Eosinophilic esophagitis (EoE) is a chronic, immune/antigen-mediated disease isolated to the esophagus and characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation.<sup>1</sup> Since its initial description in the early 1990s,<sup>2</sup> EoE has become an emerging cause of esophageal symptoms worldwide, mainly reflux-like symptoms, vomiting, abdominal pain, food refusal, and failure to thrive in infants and younger children and

## Abbreviations used

EoE: Eosinophilic esophagitis  
2-FED: Two-food elimination diet  
4-FED: Four-food elimination diet  
6-FED: Six-food elimination diet

dysphagia/food impaction in older children and young adults across westernized countries.<sup>3</sup>

The concept of food allergens as the main antigenic trigger of EoE was introduced in a seminal report published in 1995.<sup>4</sup> In this study the authors showed complete reversal of refractory esophageal eosinophilia in 8 children attributed theoretically to gastrointestinal reflux disease after being fed exclusively with an amino acid–based formula for at least 6 weeks.<sup>4</sup> Since then, numerous series have replicated the effectiveness of a dietary elimination diet for EoE in children and adults.<sup>5</sup> Unlike drug therapy (eg, proton pump inhibitors, topical corticosteroids, or both) and/or endoscopic dilation, dietary elimination therapy potentially offers an effective nonpharmacologic treatment, with continued food avoidance targeted as a long-term, drug-free disease control option. In addition, dietary therapy is the only treatment targeting the cause of the disease.

It is important to stress that initial diets are not permanent but rather a starting point. After documenting remission and subsequent individual food reintroduction, the final goal will be lifelong elimination of identified culprit foods, usually one to 3 food groups, including dairy, gluten-containing cereals, and/or eggs.<sup>5</sup> Therefore it is crucial to begin with the end in mind for both patients and physicians. This aspect should be carefully discussed between physicians, patients, and their relatives before implementing any dietary therapy in clinical practice. Likewise, the choice of dietary therapy should be negotiated with the patient or family, considering prior therapies, nutritional adequacy of baseline diet because of previous dietary restrictions related to IgE-mediated food allergy (increased risk for nutritional deprivation), patient age, family dynamics and financial resources, growth profile/rate, and potential diet-related psychological problems and patient/family preferences. Initial considerations and practical tips for elimination diets in clinical practice are summarized in Table I.

EoE is a condition mediated by allergic sensitization to food antigens, which develops in genetically susceptible subjects with predisposing early-life environmental factors through a T<sub>H</sub>2 cell–mediated immune response involving eosinophils, mast cells, and the cytokines IL-5 and IL-13.<sup>6</sup> Even though IgE sensitization to food/airborne allergens and food allergy is greater in patients with EoE, disease induction, propagation, or both have not been shown to rely on IgE-mediated mechanisms.<sup>3</sup> Therefore available blood and skin tests for food allergy are suboptimal to predict causative foods in patients with EoE, especially adults.<sup>3,6,7</sup> Empiric elimination diets, which consist of eliminating the most common food groups known to trigger EoE, have become

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**TABLE I.** Initial considerations and practical information for empiric elimination diets in clinical practice

1. Patients should begin with the end in mind. The final goal of diet will always be identifying which foods trigger esophageal inflammation to design an individualized diet with long-term avoidance of culprit food antigens, the most common being milk, wheat/gluten, and egg.
2. Ponder cautiously any elimination diet in patients who are already experiencing multiple dietary restrictions because of IgE-mediated food allergies or celiac disease.
3. Severe symptomatic patients can benefit best from topical corticosteroids. Dietary therapy can be further tested while not receiving topical steroid therapy.
4. Compliance issues with diets often arise in older children, adolescents, and young adults.
5. Provide comprehensive written information to ensure label reading is performed adequately.
6. Efficacy rates for empiric elimination diets are consistent between children and adults. Cow's milk, wheat/gluten, and eggs are the most common food triggers of EoE in children and adults from the United States, Spain, and Australia.
7. A step-up approach for empiric elimination diets might be cost-effective and improve patient uptake for dietary therapy. Therefore a 6-FED diet must be reserved for highly motivated patients unresponsive to a 2-FED or 4-FED.
8. All elimination diets should be instituted for a minimum of 6 weeks and always followed by esophageal biopsies applied during an endoscopic procedure.
9. On documented clinical and histologic remission by 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 food reintroduction.
10. Neither symptoms nor endoscopic features alone without histologic results can accurately guide the reintroduction process.
11. The reintroduction process can take up to several months. The more foods eliminated, the longer it will be. Intermittent breaks during the process are strongly recommended.
12. When available, dietary counselling by a dietitian trained in food allergies and elimination diets is advisable, especially for highly restrictive diets.

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 patients with EoE.

## DIETARY TREATMENT OPTIONS

Currently, the 3 primary choices for initial dietary therapy for EoE are an elemental diet, an empiric elimination diet, and a food allergy testing–guided elimination diet. Overall, an elemental diet remains the most effective approach (90%) for both children and adults but seems unfeasible in clinical practice.<sup>3,7</sup> A food allergy testing–guided elimination diet has shown poor consistent results in adult studies and has met success in 2 pediatric retrospective series, which have not been replicated elsewhere.<sup>3,7</sup> Finally, empiric 6-food elimination diets (6-FEDs; withdrawing milk, wheat/gluten, egg, soy, nuts, and fish/seafood) have demonstrated a consistent 72% effectiveness overall for pediatric and adult patients.<sup>3,7</sup> More recently, less restrictive dietary schemes, such as a 4-food elimination diet (4-FED; dairy, gluten-containing cereals, egg, and legumes) or a 2-food elimination diet (2-FED; dairy and gluten-containing cereals), have been developed lately with good efficacy rates. Effectiveness rates for all 3 dietary interventions in children and adults are summarized in Fig 1.

### Elemental diet

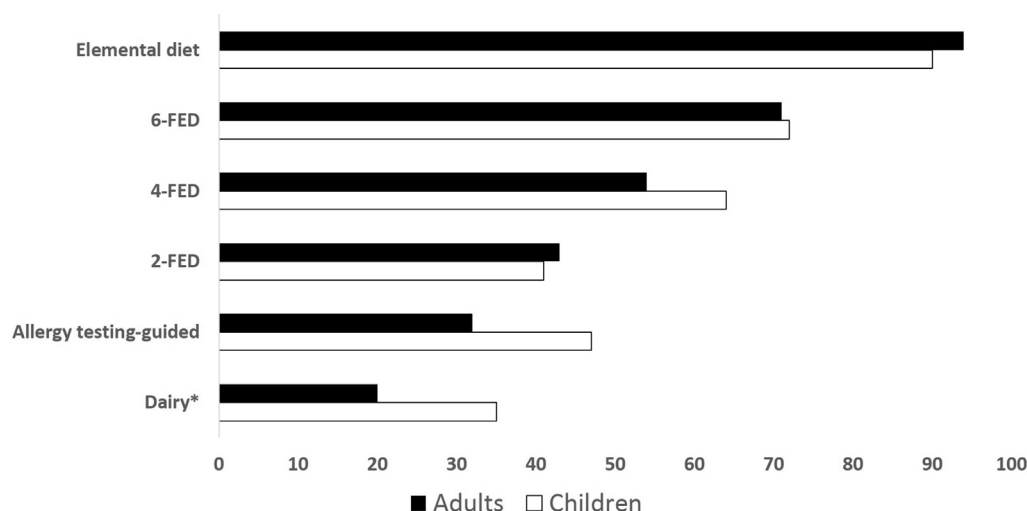
As mentioned previously, an elemental diet paved the way 25 years ago for dietary interventions in patients with EoE.<sup>4</sup> Ten children with refractory symptomatic EoE were exclusively fed an elemental formula for a minimum of 6 weeks, in which all proteins are eliminated and the nitrogen source is exclusively provided by single amino acids, thus being devoid of antigenic capacity. All patients had normalized esophageal histology, and 8 in 10 exhibited complete clinic remission as well. Since then, numerous studies, mostly retrospective in pediatric populations, corroborated these initial promising data.

Overall effectiveness was estimated in a recent meta-analysis to be around 90% in both children and adults.<sup>7</sup> However, this dietary strategy seems unfeasible in clinical practice for a variety of reasons, including its poor palatability (requiring nasogastric tubes in most children and lack of adherence in up to one third of patients recruited in recent adult prospective studies with a diet duration of 2–4 weeks<sup>8,9</sup>); social, psychologic, and quality-of-life impairment related to complete avoidance of all kinds of table food; and high cost and lack of universal coverage by health systems or insurance providers.

A potential role for an elemental diet has been proposed after failure of conventional and optimally performed therapy, either topical steroids or empiric elimination diets, in patients who wish to remain in remission while investigating the casual role of unusual foods and aeroallergens in their disease, but this approach has yet to be evaluated.<sup>3</sup> Of note, maintaining and promoting oral skills should be a priority for the duration of the elemental diet, especially in children less than 2 years of age or older children with known feeding dysfunction. When all kinds of solid foods are removed from the diet, infants and toddlers can be at risk for delayed oral-motor skill development.<sup>10</sup>

### Food allergy testing–based elimination diet

In this specific dietary approach, skin prick tests and atopy patch tests are performed to test for food allergies, with subsequent elimination of foods eliciting positive test results. A first report on the effectiveness of this strategy showed clinical and histologic remission in 49% of pediatric patients.<sup>11</sup> Mean age of patients was 5 years, and on average, 5 food groups were eliminated per patient. The main criticism to this study is that food triggers were not identified by histologic remission but rather by symptom relapse reported by parents after individual food reintroduction.<sup>11</sup> The same research group updated their results in 2012, with an overall effectiveness of 53%.<sup>12</sup> When cow's milk (the main food trigger in patients with EoE) was eliminated systematically, regardless of skin prick test/atopy patch test results, and an elemental diet was instituted in patients with diets believed



**FIG 1.** Histologic remission rates broken down by age group and shown by different modalities of dietary therapy (elemental diet, empiric elimination diet, and allergy testing-guided elimination diet) for EoE. \*Indirect data from prospective studies on 4-FEDs and 2-FEDs. Efficacy of milk elimination diets in children ranges from 33% to 56%.

to be too restrictive, the effectiveness increased up to 77%.<sup>12</sup> These results have been replicated (65% histologic remission) in just 1 retrospective study,<sup>13</sup> with much more disappointing findings in numerous pediatric studies.<sup>7</sup>

As for adult patients, poor histologic remission rates (22%<sup>14</sup> and 35%<sup>15</sup>) were reported initially with an allergy testing-based elimination diet. Beyond skin testing, a pilot study evaluated the effectiveness of a serum IgE microarray-guided elimination diet, but the study was interrupted early because of poor efficacy (7% histologic remission rate).<sup>16</sup> More recently, a comprehensive study from Australia assessed the accuracy of combining 5 different skin and blood food allergy tests to detect causative foods in adults with EoE.<sup>17</sup> 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 6-FED.<sup>17</sup> Overall, a recent meta-analysis revealed that this dietary approach led to histologic remission in 45.5% of patients, with wide heterogeneity ( $I^2 = 75\%$ ) indicating low reproducibility.<sup>7</sup> It is noteworthy that its effectiveness was significantly less in adults when compared with that found in children (32.2% vs 47.9%).<sup>7</sup>

### Novel allergy testing

Overall, cumulative data support the current thought that EoE is primarily non-IgE mediated.<sup>18,19</sup> Aside from methodological issues, discrepancies between children and adults hint at the possibility of EoE switching from an IgE-type allergy to an IgG<sub>4</sub>-type allergy as patients become adults, but this remains to be elucidated. More recently, food-specific IgG<sub>4</sub> in esophageal tissue has been evaluated recently in a small exploratory study.<sup>20</sup> Food-specific IgG<sub>4</sub> was significantly overexpressed in 20 patients with EoE compared with control subjects, confirming that an antigen-specific IgG<sub>4</sub> response can contribute to the pathogenesis of EoE. These differences were not observed in blood samples. However, no differences in food-specific IgG<sub>4</sub> levels were observed between diet responders ( $n = 11$ ) and nonresponders,

likely related to the small sample size.<sup>20</sup> Further studies evaluating this hypothesis are underway.

A novel esophageal prick test that directly challenges the esophagus with local injection of allergen extracts has been reported.<sup>21</sup> Among 8 patients with EoE, 5 showed immediate mucosal blanching and/or total luminal obstruction after mucosal injection of soy ( $n = 2$ ), banana, apple, oats, and hazelnut. In all patients luminal obstruction improved, allowing passage of the endoscopy around 10 minutes later, and was completely gone the next day.<sup>21</sup> No patient had a reaction to milk, wheat, or egg, the most common food triggers in patients with EoE. Although this study first proves the ability of the esophagus for immediate reactions after local food allergen injection, both its usefulness to guide dietary therapy and safety should be further evaluated.

### Empiric elimination diets

**6-FEDs.** The rationale for the development of this dietary strategy was based on the concept that the empiric avoidance of foods that most commonly cause immediate food hypersensitivity would also potentially resolve EoE. This diet was first tested in 2006 in pediatric patients from Chicago, in which 6 food groups that account for the majority of IgE-mediated food reactions (milk, wheat, egg, soy, nuts, and fish/seafood) were eliminated for 6 weeks.<sup>22</sup> The 6-FED led to clinical and histologic remission in 74% of children in this first seminal study, with no inferiority compared with an elemental diet. Quite similar results have been replicated further in pediatric<sup>13,23</sup> and adult<sup>15,24-29</sup> populations. A detailed summary of prospective studies evaluating the efficacy of a 6-FED is shown in Table II.<sup>23-30</sup> A meta-analysis revealed that this dietary approach provided an extremely homogeneous ( $I^2$  statistic = 0) 72% histologic remission in both children and adults.<sup>7</sup>

The most common causative foods identified after response to a 6-FED have been by far cow's milk, followed by wheat/gluten, egg, and, to a lesser extent, soy/legumes (with the exception of studies conducted in Spain, where legumes, such as lentils, chickpeas, or peas, are consumed regularly).<sup>25,28,30</sup> On the

**TABLE II.** Comprehensive information in prospective studies evaluating the efficacy of the empiric 6-FED, 4-FED, and 2-FED

First author, year of publication, country	Diet/population/design	Histologic remission	No. of culprit foods identified through individual reintroduction of either 6, 4, or 2 food groups			Most common food triggers identified through individual food reintroduction
			1	2	>2	
Kagalwalla et al, 2011, United States <sup>23</sup>	6-FED/children/unicenter	74%	72%	8%*	8%*	Milk = 74% Wheat = 26% Eggs = 17%
Gonsalves et al, 2012, United States <sup>24</sup>	6-FED/adults/unicenter	70%	85%	15%*		Wheat = 60% Milk = 50%
Lucendo et al, 2013, Spain <sup>25</sup>	6-FED/adults/unicenter	72%	36%	31%	33%	Milk = 62% Wheat = 29% Egg = 26% Legumes = 24%
Rodriguez-Sanchez et al, 2014, Spain <sup>26</sup>	6-FED/adults/unicenter	53%	—	—	—	Milk = 64% Wheat = 28% Egg = 21% Legumes = 7%
Philpott et al, 2016, Australia <sup>27</sup>	6-FED/adults/unicenter	52%	56%	17%	13%	Milk = 43% Wheat = 43% Egg = 34%
Molina-Infante et al, 2014, Spain <sup>28</sup>	4-FED/adults/multicenter	54%	45%	45%	—	Milk = 50% Egg = 36% Wheat = 31% Legumes = 18%
Kagalwalla et al, 2017, United States <sup>29</sup>	4-FED/children/multicenter	64%	64%†	20%†	16%†	Milk = 85% Egg = 35% Wheat = 33%
Molina-Infante et al, 2017, Spain <sup>30</sup>	2-FED/children and adults/multicenter	43%	68%	28%	0%	Milk = 52% Milk and wheat = 28% Wheat = 16%
Molina-Infante et al, 2017, Spain <sup>30</sup>	Combined effective 2-FED plus 4-FED/nonresponders/multicenter	60%	10%	60%	30%	Milk = 90% Egg = 60% Legumes = 40% Wheat = 30%
Molina-Infante et al, 2017, Spain <sup>30</sup>	Combined effective 2-FED and 4-FED plus 6-FED/nonresponders/multicenter	79%	0%	0%	100%	Egg = 100% Fish-seafood = 100% Milk = 75% Wheat = 75% Legumes = 50% Nuts = 25%

\*Not every dietary responder patient underwent complete food reintroduction.

†Percentages referred to the subgroup of 25 children who completed all foods.

contrary, all studies have consistently shown that nuts and fish/seafood rarely trigger EoE (Table II). Thus studies on 6-FEDs have been instrumental to decipher the most common food triggers in patients with EoE, but on the other hand, the high level of dietary restriction and numerous endoscopies required have been the best deterrent for patients and physicians to engage with dietary therapy. Interestingly, up to three quarters of responders in 6-FED studies were found to have just 1 or 2 causative foods after 6-food challenges and 6 endoscopic procedures (Table II). As such, it was predictable that less restrictive dietary schemes, eliminating the most common food triggers and reducing the number endoscopic procedures, could provide efficacy rates closer to those observed with a 6-FED.

**Four-food elimination diet.** On the aforementioned basis intended to optimize dietary restrictions and endoscopic procedures for dietary therapy, the 4-food elimination diet (4-

FED) was developed, avoiding the most common food triggers in patients with EoE (animal milk, gluten-containing cereals, eggs, and legumes).<sup>27</sup> A first prospective multicenter study conducted in 52 Spanish adults with EoE showed a 54% remission.<sup>28</sup> Half of adult responders to 4-FEDs were found to have milk, gluten, or both as food triggers, and therefore theoretically, they could have been identified with a 2-FED by eliminating milk and gluten without egg or legume restriction. As for children, a first multicenter study in 78 patients from the United States has been reported recently.<sup>29</sup> The histologic remission rate was even greater than in adults (64%). The most common food triggers were cow's milk (85%), egg (35%), wheat (33%), and soy (19%). It is noteworthy that 55% of pediatric responders to a 4-FGED had cow's milk as the only food trigger after individual food reintroduction. Detailed information about both studies is displayed in Table II.

**TABLE III.** Unsolved issues in dietary therapy for EoE

Related to eliminated foods	
Cross-reactivity issues	Cow's milk vs mammalian milk
	Wheat vs gluten-containing grains
	Soy vs all legumes (Mediterranean countries)
	Cross-reactivity between foods and airborne allergens
Elimination diet duration	Six, 8, 12 weeks, or beyond?
Milk elimination diet	Prospective studies in children and adults are warranted
Dependence on different patterns of food consumption across the world	Should different diets be applied according to local food consumption patterns? Will EoE food triggers be different in nonwesternized countries?
Related to individual food reintroduction	
Need for standardization <sup>33</sup>	Individual reintroduction one at a time
	Reintroduce all eliminated foods
	Order of reintroduction?
	Duration: 6, 8, 12 weeks, or beyond?
	A shorter timeframe if symptoms develop on food challenge?
	Washout periods after positive challenge result? For how long?
Loss of tolerance to eliminated antigens showing high baseline IgE titers	Risk of IgE-mediated allergic reactions
Related to repeat endoscopic procedures	
	Safety of repeat propofol sedation
	Validation of minimally invasive procedures (String Test, Cytosponge) for food reintroduction
Related to the development of novel food allergy testing for EoE	
	Esophageal prick test?
	IgG <sub>4</sub> -based local methods?
	Genetic profiling?
Related to long-term efficacy	
	Long-term response in adherent patient
	Loss of response because of airborne allergens
	Spontaneous development of tolerance to culprit food antigens?
	Tolerance induction with baked foods?
Related to EoE development after oral immunotherapy	
	Individual risk factors for having <i>de novo</i> EoE after oral immunotherapy
	Best option to solve EoE: eliminating the responsible food (and assuming the risk of further IgE-mediated reactions) or managing EoE with drugs?

**Step-up approach: 2-4-6.** If among responders to a 4-FED half of adults could have been identified with a simplified 2-FED (milk and gluten)<sup>28</sup> and 56% children with an even simpler 1-food elimination diet (milk),<sup>29</sup> a step-up approach for dietary therapy in patients with EoE (ie, eliminating at first the 1 or 2 most common food triggers and subsequently increasing the level of restriction in nonresponders) could result in notable advantages, such as reducing dietary restrictions, endoscopic procedures, costs, and shortening the diagnostic process. This approach has been first assessed in a multicenter study conducted in 14 centers, mostly from Spain, gathering 130 consecutive patients, of whom 25 were children.<sup>30</sup> In this study all patients underwent a 2-FED (milk and gluten), and nonresponders were offered to escalate to a 4-FED and eventually to a 6-FED if no response was observed. A 2-FED achieved EoE remission in 43% of patients, without differences between pediatric and adult patients. In nonresponders to a 2-FED, stepping up to a 4-FED (60%) and a 6-FED (79%) led to similar remission rates previously reported. Compared with starting with a 6-FED, this step-up strategy allowed reduction of endoscopic procedures and shortening of the diagnostic process time by 20%.<sup>30</sup> Moreover, dietary restrictions for patients were notably optimized because 43% of included patients with EoE could know their triggering foods without eliminating egg, legumes, nuts, and fish/seafood, up to 60% while consuming nuts and fish/seafood. Additionally, 90% of responders to a 2-FED or 4-FED had 1 or 2 causative food groups, thus identifying responders with few food triggers without need of

a 6-FED. These responders with few food triggers for EoE are definitively the best candidates for maintenance dietary therapy. It is interesting to note that responders to a 6-FED with previous failure of a 2-FED and 4-FED had 3 or more food triggers, including nuts and fish/seafood. 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.<sup>30</sup> Taking these results into consideration, a 6-FED might be reserved currently for motivated patients unresponsive to less restrictive empiric elimination diet schemes who are still willing to elucidate their food triggers. Last but not least, the results obtained with this step-up approach study might definitely improve patient acceptance of dietary therapy, which makes it much more easier and doable compared with a 6-FED. Overall, the most common food triggers identified in all prospective empiric elimination diet studies (either 6-, 4-, or 2-FEDs) are shown in [Table II](#).

**Cow's milk elimination diet.** Because cow's milk has been reported to be the most common food trigger, especially in children, a cow's milk elimination diet would be an easier way to check the efficacy of dietary intervention. A cow's milk elimination diet in children has been reported recently in 2 studies.<sup>31,32</sup> Despite encouraging histologic remission rates (65%<sup>31</sup> and 61%<sup>32</sup>), both studies might be flawed by methodological issues.

For the first study, patients included were children with IgE-mediated cow's milk food allergy after cow's milk oral desensitization.<sup>31</sup> Aside from not being representative of a standard



population of pediatric EoE, cow's milk oral immunotherapy-induced EoE is always responsive to a cow's milk elimination diet.<sup>33</sup>

Regarding the second study, proton pump inhibitors were given concomitantly with dietary therapy, which might have overestimated histologic remission rates. Up to 50% of pediatric and adult patients can achieve EoE remission with proton pump inhibitor monotherapy.<sup>3</sup>

Indirect estimations from 4-FEDs and 2-FEDs have shown that histologic remission with a milk elimination diet can be accomplished in 18%<sup>30</sup> and 25%<sup>28</sup> of adult patients, whereas these figures seem to be greater in children (33%,<sup>30</sup> 56%<sup>29</sup>). Prospective studies specifically designed to assess the efficacy of a milk elimination diet in children and adults are definitely warranted.

### LONG-TERM EFFICACY AND SAFETY OF DIETARY THERAPY

Once food triggers responsible for EoE have been identified in each patient, long-term avoidance is advisable to maintain drug-free disease remission. Presently, we have only few short-term data on this matter. A first study in children demonstrated that after effective long-term avoidance of food triggers (of up to 4 years), all cases relapsed on rechallenge with food triggers.<sup>23</sup> Two studies in adults have consistently reported that all compliant patients who strictly avoided a food or foods known to trigger the disease continued with clinical and histologic remission for a period of up to 3 years.<sup>24,25</sup> Two more recent studies in adults have confirmed that all patients who remain compliant with avoidance of the identified food triggers after an elimination diet maintain histologic remission after 1 year.<sup>27,34</sup> Studies with longer follow-up of diet responders are required to clarify the role of maintenance dietary therapy in patients with EoE.

As for safety, there are controversial data in the literature regarding the effect of elimination diets on anthropometric profiles and growth in children and adults with EoE.<sup>35</sup> It is important to stress that children with IgE-mediated food allergies, a common comorbid condition in pediatric EoE, and avoiding more than 3 food groups might be at high risk of impaired growth.<sup>35</sup> Weight loss and growth rates should be assessed before initiating any therapeutic elimination diet and closely monitored afterward. Although there are no studies available on this issue, low macronutrient (especially fats in milk- and egg-free diets and carbohydrates in milk- and wheat-free diets), low fiber (in cereal- and legume-free diets), and low micronutrient (calcium, vitamin D, B vitamins, and iodine in milk-, wheat-, and egg-free diets) intake should be assessed regularly during follow-up.<sup>35</sup> Similar to the FODMAP diet,<sup>36</sup> the effect of milk, wheat, and legume avoidance on intestinal microbiota as a result of reducing sources of prebiotic carbohydrates to the gut also deserves further consideration. When available, the involvement of a dietitian trained in food allergies and elimination diets used in the management of EoE should be considered an invaluable asset to manage dietary therapy.<sup>37</sup>

### UNMET ISSUES WITH DIETARY THERAPY IN PATIENTS WITH EoE

Numerous unsolved issues yet related to elimination diets in patients with EoE have been summarized in Table III.<sup>33</sup> The precise correct duration of the initial elimination diet remains

unknown, but 6 weeks seems to be a minimum. Because of cross-reactivity between cow's milk and other mammalian milks or wheat and other gluten-containing grains, whether just cow's milk and wheat should be eliminated or also all potential cross-reactive foods remains debatable.<sup>38</sup> Once remission of eosinophilic inflammation is achieved with an elimination diet, individual reintroduction of food or food groups 1 at a time should be undertaken for a minimum of 6 weeks. The accurate duration of the food challenge remains unknown. Similarly, the frequency and serving size of the challenged food per week remains to be elucidated. Losing IgE tolerance to foods after elimination diets and subsequent allergic IgE-mediated reaction is a potential concern. Isolated symptoms or endoscopic signs should not guide the reintroduction process because of the poor correlation of both with histologic remission.<sup>3</sup> Because of the lack of noninvasive biomarkers that can adequately predict the presence or absence of esophageal eosinophilic inflammation, multiple endoscopies with systematic biopsy specimens are currently mandatory to accurately identify food triggers. Acceptance of this strategy and reuptake of patients is largely conditioned by providing systematic sedation for endoscopic procedures, along with flexibility to schedule and reschedule endoscopic appointments, depending on histologic results. The long-term safety of repeated procedural sedation remains unknown.

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