

# Dietary Management of Eosinophilic Esophagitis

## Man Versus Food or Food Versus Man?

Joy W. Chang, MD, MS<sup>a,\*</sup>, Emily Haller, MS, RDN<sup>a</sup>,  
Evan S. Dellon, MD, MPH<sup>b</sup>

### KEYWORDS

• Eosinophilic esophagitis • Food antigens • Diet elimination • Treatment

### KEY POINTS

- An elimination diet is an effective first-line treatment for the long-term management of eosinophilic esophagitis and offers patients a nonpharmacologic alternative to disease control.
- Empiric elimination approaches are favored over allergy test-based approaches.
- Partnering with a dietitian or nutritionist is important to maximize adherence to and success of this treatment modality.

### INTRODUCTION: FOOD VERSUS MAN

Eosinophilic esophagitis (EoE) is a recently recognized chronic inflammatory disease of both children and adults, characterized by symptoms of esophageal dysfunction and eosinophilia, which can lead to sequelae of fibrosis and strictures.<sup>1-3</sup> Since EoE was first described nearly 30 years ago, the prevalence and incidence have rapidly increased to as many as 1 case per 1000 people and up to 12.8 per 100,000 new cases per year, respectively.<sup>4-6</sup> EoE is now one of the most common causes of dysphagia, diagnosed in up to one-half of adults with an esophageal food impaction, up to 23% undergoing endoscopy for dysphagia, and up to 8% for the indication of reflux.<sup>7-9</sup> The clinical presentation in children can vary and include feeding difficulties, failure to thrive, vomiting, abdominal pain, and more typical reflux symptoms. Epidemiologic studies suggest that there are environmental and early life risk factors

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<sup>a</sup> Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Michigan, 3912 Taubman Center, 1500 E. Medical Center Drive, SPC 5362, Ann Arbor, MI 48109, USA; <sup>b</sup> Division of Gastroenterology and Hepatology, Department of Internal Medicine, Center for Esophageal Diseases and Swallowing, University of North Carolina School of Medicine, CB #7080, Bioinformatics Building, 130 Mason Farm Road, Chapel Hill, NC 27599, USA

\* Corresponding author.

E-mail address: [chjoy@med.umich.edu](mailto:chjoy@med.umich.edu)

Twitter: [@JoyWChang](https://twitter.com/JoyWChang) (J.W.C.)

**Table 1**  
**Pooled response rates for various diet therapy strategies**

	Pediatrics	Adults
Elemental diet	90%	94%
6-food empiric elimination diet	73%	71%
4-food empiric elimination diet	60%	46%
2-food empiric elimination diet	43%	
1-food empiric elimination diet (milk only)	66%	100%
Targeted diet	48%	32%

Data from Arias A, Gonzalez-Cervera J, Tenias JM, et al. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. *Gastroenterology* 2014;146:1639-48 and Molina-Infante J, Arias A, Alcedo J, et al. Step-up empiric elimination diet for pediatric and adult eosinophilic esophagitis: The 2-4-6 study. *J Allergy Clin Immunol* 2018;141:1365-1372.

including aeroallergens, Cesarean delivery, prematurity, antibiotics, and formula feeding.<sup>10,11</sup> Similar to trends in other allergic disorders, the recent increase in EoE prevalence and incidence may also be related to changes in food processing. EoE is frequently associated with other atopic diseases including allergic rhinitis, asthma, eczema, and food allergies, suggesting common disease mechanisms.<sup>12</sup> EoE is a Th2-mediated response to food allergens, but does not seem to be IgE mediated.<sup>13</sup>

Current first-line treatments for EoE include diet elimination or medications (eg, proton pump inhibitors [PPI] and topical corticosteroids), with therapeutic goals of histologic, endoscopic, and symptomatic improvement.<sup>14</sup> Because the eosinophil-predominant inflammation is precipitated by food antigens (ie, food vs man), a dietary approach to treatment involving the avoidance of food triggers (ie, man vs food) has become an effective and acceptable long-term therapy for EoE. Since this concept was first validated in a landmark study reporting complete resolution of esophageal eosinophilia on an allergen-free formula, several prospective studies demonstrate the success of dietary elimination. The goal of EoE diet therapy is to induce disease remission by removing a set of foods from the diet, then systematically reintroducing single foods or food groups to identify which triggers to avoid in the long term (Fig. 1). Ideally, a smaller number of foods are initially eliminated, thus minimizing the amount of restrictions. Depending on a patients' individual values, attitudes, preferences, resources, and motivation, diet therapy can be an appealing option over pharmacologic treatments. The three dietary strategies for EoE include elemental diet, empiric elimination diet, and targeted elimination diet (Table 1).

## TREATMENT OPTIONS: MAN VERSUS FOOD

### *Elemental Diet*

As the first proof of concept that food antigens play a role in the pathogenesis of EoE, hypoallergenic amino acid–based elemental formula was shown to induce clinical and histologic remission in children.<sup>15</sup> This finding was validated by additional pediatric studies reporting histologic remission in up to 96%.<sup>16,17</sup> Later studies in adults also demonstrated significant improvement in esophageal eosinophilia and symptoms in up to 72% of patients.<sup>18,19</sup> A meta-analysis by Arias and colleagues<sup>20</sup> found a pooled histologic response rate to elemental formula of 91%. However, notable challenges in applying this diet include the need for an enteric feeding tube, poor palatability of the formula, and high financial cost because these feeds are often not covered by insurance. Additionally, food reintroduction is challenging because all foods have been

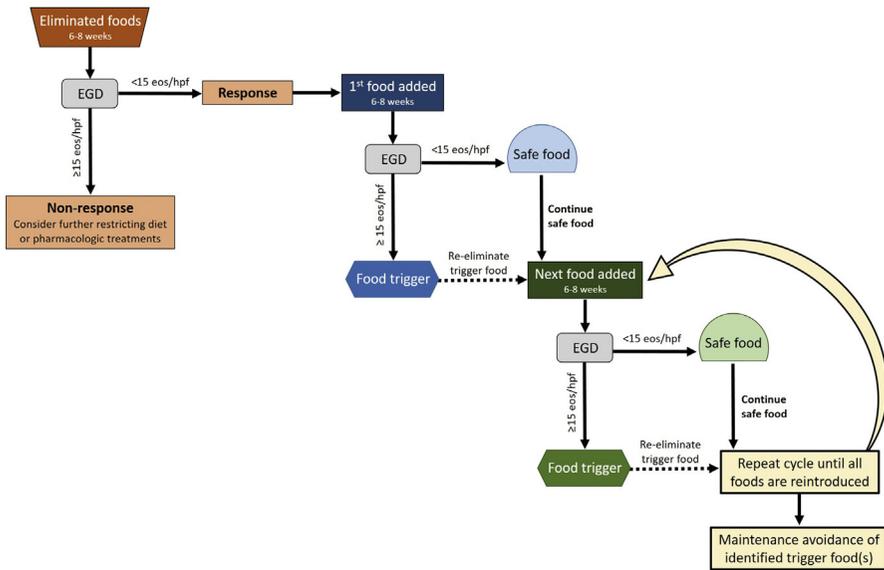


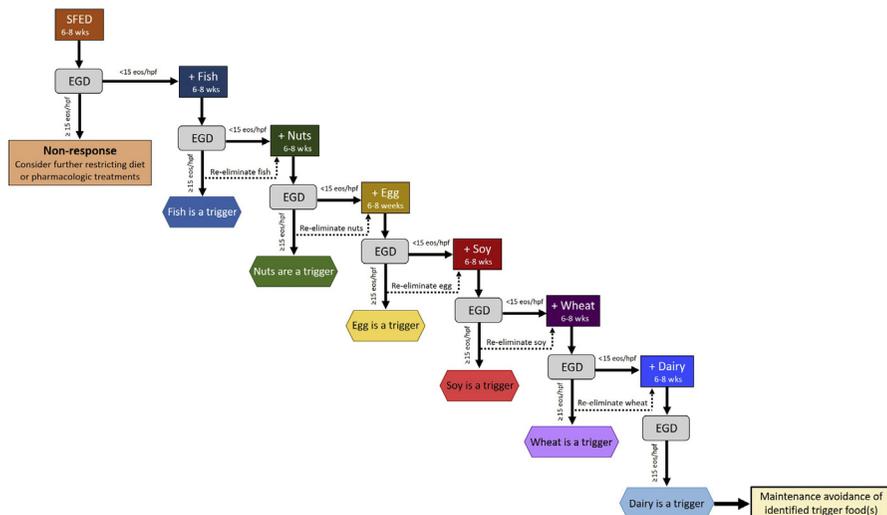
Fig. 1. Empiric elimination and reintroduction strategy.

eliminated, and thus must be sequentially added back. Although there are no standardized guidelines for the use of an elemental diet, we recommend gradual food reintroduction and identification of potential food triggers once histologic remission is demonstrated on an exclusively elemental diet for 4 to 6 weeks. In this setting, food groups that are thought to have a low trigger potential (ie, nonlegume vegetables, fruits, rice) can be added sequentially before an endoscopy, leaving more allergenic foods (ie, legumes, milk, egg, soy, wheat, nuts, meat, fish and shellfish, and corn) to be individually added last.<sup>21</sup>

### Empiric Elimination Diets: Elimination, Reintroduction, and Maintenance

#### Six-food elimination diet

In contrast with the highly restrictive elemental formula approach, a more attractive and feasible option is empiric elimination. This approach focuses on inducing disease remission by removing the most common food triggers, systematic food reintroduction, and ultimately, avoidance of only the specific trigger(s) to maintain long-term disease control. The 6-food elimination diet (SFED) with avoidance of dairy, wheat, soy, eggs, nuts, and seafood is the prototypical empiric elimination diet in the United States (Fig. 2). In Spain, investigators using the SFED further eliminate cereal grains (eg, wheat, barley, rye, oats, rice, corn) and legumes. Kagalwalla and colleagues<sup>22</sup> first demonstrated a response rate of 74% with SFED (vs 88% on elemental diet) in children. Since then, success in attaining histologic remission on the SFED has been validated in children (ranging from 50% to 81%) and adults (ranging from 52% to 73%),<sup>17,23-25</sup> with a pooled rate of 72%.<sup>20</sup> Once patients have demonstrated resolution of eosinophilic inflammation and symptom improvement on the full elimination diet, each food group is sequentially added back beginning with the least allergenic, followed by endoscopy with biopsy to monitor response to food reintroduction. Ultimately, the goal of the elimination diet is to identify the particular food triggers that a patient should avoid to achieve long-term disease and symptom control. Guidance with a licensed dietitian is instrumental in providing education and practical tips to succeed and is recommended during all phases of diet therapy. Although the elimination diet is an effective strategy to attain drug-free disease control, downsides include



**Fig. 2.** Empiric SFED protocol. (Adapted from Kagalwalla AF, Wechsler JB, Amsden K, et al. Efficacy of a 4-Food Elimination Diet for Children With Eosinophilic Esophagitis. Clin Gastroenterol Hepatol 2017;15:1698-1707.)

adherence to a strict diet initially, at least 7 endoscopies to determine treatment response and food triggers, and long-term compliance with dietary trigger avoidance.

#### Four-food elimination diet

Since the introduction of the SFED, milk and wheat have been identified in food reintroduction studies as the most common EoE triggers and less commonly, nuts and fish/shellfish.<sup>26</sup> As a result, the 4-food elimination diet (4FED), which removes dairy, wheat, egg, and soy, was developed as an effective alternative with less dietary restrictions and fewer endoscopies to identify potential food triggers. Success with 47% histologic response ( $\leq 5$  eos/hpf, 60% with  $\leq 10$  eos/hpf) and 40% symptom improvement was achieved in a clinical study of children and adults undergoing 4FED.<sup>27</sup> A prospective study of adult Spanish patients with EoE avoiding milk, wheat, eggs, and legumes reported 54% clinicopathologic response and among those, milk was identified as the trigger in one-half of the participants.<sup>28</sup> In parallel, a prospective study of American children on the 4FED avoiding milk, wheat, egg, and soy demonstrated 64% response rates for histologic remission and symptom improvement in 91%.<sup>29</sup> Among these children, reintroduction phases showed that milk was the most common trigger in 85%, followed by egg (35%) and wheat (33%).

#### The 2-4-6 step-up diet

In an attempt to make EoE dietary elimination more patient-friendly, the Spanish group developed a “step-up” approach, beginning with elimination of milk and wheat or “2-food” elimination. This approach allows patients to avoid the most common food triggers first, and only move to additional restriction if there is nonresponse. In a prospective study of Spanish adults and children, 2-food elimination of milk, wheat, and gluten yielded a 43% clinical and histologic response rate.<sup>30</sup> Nonresponders were stepped up to increasingly restrictive diets (4FED and SFED) and subsequent remission rates were 54% for 4FED, and 79% for SFED. compared with starting with empiric SFED, this step-up strategy improves the time and number of endoscopies required by 20% to 30% and offers an efficient option for patients electing diet therapy. It is important to note, however, that at each step-up in restriction a proportion of patients opted

to not continue with the protocol and sought out other treatments. Therefore, the response rates in the 4FED and 6FED groups are reflective of highly motivated and adherent patients.

### ***Milk elimination***

Because milk is the most common EoE trigger, dairy exclusion or a 1-food elimination diet (1FED) is also a reasonable approach in diet therapy. An early retrospective study of pediatric patients with EoE undergoing cow's milk elimination reported histologic and clinical remission in 65%.<sup>31</sup> This finding was further validated by prospective pediatric studies showing histologic response rates ranging from 43% to 64% to cow's milk elimination, presenting the possibility for an even more abbreviated and less burdensome option to diet therapy.<sup>32–34</sup> A recent multisite prospective randomized clinical trial of children undergoing 12 weeks of 1FED versus 4FED reported that, although symptom improvement was found to be greater in the 4FED, the histologic response rates were similar between the 2 diets (44% for 1FED, 41% for 4FED). Furthermore, quality of life was improved with 1FED compared with 4FED.<sup>35</sup> Success with exclusive milk elimination was also reported in a recent retrospective study of pediatric patients attaining histologic remission in 57% with 1FED compared with 52% with SFED.<sup>36</sup> For adults, a multisite randomized clinical trial of 1FED versus SFED is currently underway (NCT02778867) and may further highlight dairy elimination as a reasonable first treatment option in EoE. Finally, there has been one modeling study that attempted to clarify an optimal empiric elimination approach based on published food trigger data.<sup>37</sup> This study suggested that a “1 to 3” diet, where dairy is eliminated first and then wheat and eggs are additionally eliminated if there is no response to dairy, and a “1-4-8” diet, which steps up from dairy, to 4FED, and then to an additional elimination of corn, chicken, beef, and pork, are optimal depending on the treatment goal (most effective response, which is 1-4-8, or least number of endoscopies, which is 1–3). However, these strategies have yet to be tested clinically.

### ***Concomitant Proton Pump Inhibitor Therapy***

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For patients who prefer a medication-free approach to treatment, the empiric elimination diet is often prescribed without concurrent pharmacologic therapies. PPIs are also a first-line treatment and estimated to be effective in up to half of patients with EoE.<sup>38</sup> In a recent Australian multisite clinical trial, histologic remission was higher in pediatric patients receiving PPI plus 4FED (88%) versus PPI alone (45%).<sup>39</sup> Similarly, children who received PPI with a dairy-free diet demonstrated higher histologic response rates (61%) compared with those treated with dairy-free diet alone (25%).<sup>36</sup> This result suggests there might be a synergistic effect between diet and PPI treatment, but the mechanism of this effect is not known.

### ***Targeted Elimination Diet***

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In contrast with empiric elimination of common EoE food triggers, targeted elimination diet is avoidance of foods identified by traditional allergy testing such as a skin prick test, atopy patch test, or serum-specific IgE testing. This would seem to make intuitive sense; if EoE is a food-triggered disease, then allergy tests should identify the food trigger. Indeed, initial studies in children demonstrated response rates ranging from 53% to 72% using a skin prick test and an atopy patch test.<sup>17,40</sup> In contrast, more recent data showing low responses from 12% to 37% to an atopy patch test in children with EoE has put the benefit of allergy testing for EoE in question.<sup>41–43</sup> Adult studies also showed poor concordance (13%) between the skin prick test and identified EoE trigger foods.<sup>24,25,44,45</sup> In the meta-analysis by Arias and colleagues,<sup>20</sup> the

pooled response rate to targeted elimination was 46%, lower than either elemental formula or SFED. As a result of these findings suggesting that conventional allergy testing is unreliable to identify EoE triggers, this process is no longer recommended as a dietary approach to EoE treatment and may be detrimental if patients are prescribed strict or overly restrictive diets based on testing.

### **CHALLENGES OF DIETARY THERAPY: FOOD VERSUS MAN**

Although diet therapy is an effective means of maintaining disease control by addressing the root cause of food antigens in EoE, several challenges in adopting this treatment strategy are worth mentioning. Practical downsides to elimination diets include adherence to a strict diet and frequent endoscopies initially, financial costs and burden of a special diet, long-term compliance with dietary trigger avoidance, and potential losses in quality of life.

#### ***Cost and Burden***

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For the long-term management of celiac disease, the increased cost of commercially available gluten-free products is estimated to range from 183% to 242% more expensive compared with regular foods.<sup>46,47</sup> Along similar lines, the empiric elimination diet for EoE includes the exclusion of ubiquitous and commonly consumed food groups and purchase of specialty foods, resulting in significant financial costs and burden to patients. From a payer perspective, the SFED is reported to be more cost effective than topical corticosteroids, likely owing to the high cost of long-term medication use. However, this factor does not account for patient-level food costs not covered by insurance or decrements in quality of life.<sup>48,49</sup> Perhaps more impactful, a study of real-world patient-level costs using grocery store prices showed that adherence to an SFED costs \$650 per year more than an unrestricted diet.<sup>50</sup> Additionally, purchasing foods for an SFED required visiting more than one grocery or specialty store, increasing the shopping burden for patients and families. Other notable but less observed costs include days of missed work or school for both patients and caregivers, as well as increased insurance costs.<sup>51</sup>

Because clinical symptoms do not correlate well with esophageal inflammation and underlying disease activity, endoscopy with esophageal biopsies is recommended to guide decisions about treatment.<sup>52,53</sup> The empiric elimination diet and systematic food reintroduction requires frequent endoscopies to monitor response and determination of food triggers. Patients undergoing SFED ought to expect a minimum of six endoscopies over one year's time, but this process can be prolonged with more procedures if food triggers are identified during reintroduction, reflecting a significant burden on time and convenience on both patients and their families.

#### ***Nonresponse to Diet Therapy***

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Although diet therapy can be an effective treatment for EoE for many, several factors may impact either symptomatic or histologic response and should be considered in the nonresponsive patient. Nonadherence to the diet is perhaps the most obvious cause, which may be due to the increased financial cost of dietary alternatives, lack of knowledge and support, lack of positive results, or a desire to consume trigger foods. Cross-contamination can also occur and may be prevented or minimized with guidance from a dietitian. Finally, because current treatment end points include improvement of symptoms, endoscopic findings, and histology, persistent fibrostenotic disease and stricture management with endoscopic dilation should be considered in the setting of ongoing symptoms despite histologic remission. Conversely, in patients who report subjective symptom improvement but fail to attain histologic

remission, a detailed history about recent dilation and modified eating behaviors should be further investigated. Finally, there is one report that some patients with initial symptomatic and endoscopic, but no histologic, improvement may benefit from an extended course of dietary elimination, and ultimately achieve remission after at least 12 weeks of dietary adherence.<sup>54</sup>

### ***Adherence and Long-Term Effectiveness***

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Despite the effectiveness of diet therapy, long-term avoidance of food triggers can be burdensome, resulting in nonadherence and recurrence of disease activity. The short-term effectiveness of diet exclusion is well-established, but response rates may wane owing to decreased adherence. Studies of long-term follow-up outcomes of the SFED in up to three years report that less than one-half of patients sustain histologic response owing to nonadherence to the diet,<sup>24,55–57</sup> although one study does report excellent long-term remission rates.<sup>25</sup> Factors impacting adherence to diet therapy include treatment effectiveness, limitations of social situations, and anxiety related to the diet.<sup>57</sup>

### ***Quality of Life***

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Patients with EoE experience impaired quality of life, not only from symptoms, but also around eating, social, and emotional impacts, as well as anxiety around their disease and choking.<sup>58–60</sup> Treatments significantly improve quality of life, but the burdens of the treatments themselves are often overlooked. Although initial study of adults undergoing SFED showed increase in overall quality of life as measured with the Short Form-36, individual mental well-being scores decreased.<sup>24</sup> Similarly, the mental component score of the Short Form-36 assessment was lower in adult patients with EoE undergoing empiric elimination diet.<sup>61</sup> In a prospective study of adult Spanish patients with EoE, emotional impact was significantly worse in those undergoing dietary restriction, but the overall quality of life scores were not significantly worse compared with those without restriction and undergoing pharmacologic therapies.<sup>62</sup> In the pediatric population, children treated with diet reported lower quality of life scores,<sup>63,64</sup> highlighting realistic psychosocial concerns about initiating restrictive diets in young patients.

### ***Access to Other Support***

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Because implementing diet therapy can be challenging for both patients and clinicians, we recommend that all patients attempting an elimination diet do so with the support of a dietitian. Dietitian support is critical, not only to improve diet adherence during the elimination phase, but also to provide personalized education and practical guidance on how to maintain a nutritionally balanced and palatable diet. Despite increasing interest in dietary interventions for several gastrointestinal diseases, such as irritable bowel syndrome, inflammatory bowel disease, and gastroesophageal reflux disease, many patients and providers realistically may not have access to a dietitian or nutrition resources, and many gastroenterology providers (especially those caring for adults) may not have had adequate training in nutrition and face time constraints during clinic visits to provide patient support. In a recent provider survey, only 65% of respondents reported having readily available support with a licensed dietitian when recommending diet therapy.<sup>65</sup> In parallel, only 36% patients with eosinophilic gastrointestinal disorders reported having easy access to a dietitian or nutritionist who understood the challenges of eosinophilic gastrointestinal disorders.<sup>66</sup>

Although the use of allergy testing to guide elimination diets has been supplanted by empiric elimination diets, clinical support by an allergist for patients with concomitant atopic disorders is very helpful in the management of EoE. This is particularly true

given the high prevalence of atopy in children and adults with EoE including allergic rhinitis, asthma, and atopic dermatitis. Additionally, a multidisciplinary approach between the gastroenterologist and allergist may be advantageous for concomitant IgE mediated food reactions and potentially in unique cases of nonresponse to the empiric elimination diet.

### **PRACTICAL TIPS AND CONSIDERATIONS FOR STARTING DIET THERAPY**

When considering starting treatment for EoE, all options including diet, pharmacologic therapy (e.g. PPI, topical corticosteroids), and endoscopic dilation ought to be presented to the patient. Success with an elimination diet depends on both patient selection and ability execute the avoidance and food reintroduction phases.

#### **Considerations in patient selection for diet therapy**

- Patient's desire and motivation to undergo diet therapy
- Personal preferences and values
- Patient's age, life stage, living situation, lifestyle (e.g. ability to adhere to a strict diet)
- Patient's willingness to have frequent endoscopies and travel
- Patient's finances and insurance coverage (e.g. high deductibles for procedures)

#### ***Practical Aspects of Applying Diet Therapy for Initial and Maintenance Treatment***

When working with a registered dietitian, commonly addressed patient concerns include ensuring the diet is healthy and meets nutrient needs, travel and dining out tips, what foods are allowed and specific product options, cross-contamination, and nutrition label reading.

#### **Navigating the supermarket**

- Where to shop, specific to patient location and access
- Use of online ordering/shopping for specialty items if or as desired
- Food labels: education on the Food Allergen Labeling and Consumer Protection Act, which mandates that companies list foods containing major allergens including milk, wheat, eggs, fish, shellfish, peanuts, tree nuts, and soy in plain language.
- Review of precautionary labeling (i.e. May contain [fish]; Manufactured in a facility that uses [egg] ingredients; Manufactured in a facility which processes [egg])

#### **Dining out and social events**

- Doerfler's "Dining Out Checklist"<sup>67</sup>
- Bring a dish or appetizer of safe foods
- Shift the focus away from food and toward an activity

#### **Nutritional implications of diet therapy**

- Ensure macronutrient and micronutrient needs are met
- Provide hypoallergenic multivitamin recommendations, potential use of vitamin D and/or calcium supplements

#### **Diet "holidays"**

- During the diet therapy trial there may be times after a patient completes a reintroduction that they need a break or "diet holiday" and may need to lift their diet restrictions. If this happens, endoscopy must be scheduled 6 to 8 weeks out from when they resume the diet.
- If the patient is responsive to both diet therapy and medications, they may also elect to switch between the 2 treatment modalities for periods of time depending on life events and situation (e.g. around traveling or holidays if known food allergens may be consumed).

### What to expect during dietitian-guided EoE diet therapy

#### Initial visit with dietitian consists of (1-hour visit)

1. Thorough diet history including a patient's food preferences, eating habits, known food allergies and intolerances, a diet recall of typical a weekday and weekends, symptoms (i.e. dysphagia), vitamin/mineral and supplement use.
2. Nutrition education
  - Comprehensive review of avoiding food allergens (e.g. 2-, 4-, SFED) that will need to be avoided and individualized dietary advice. Recommendations of what to eat should be customized to a patient's food preferences, cooking knowledge and skills, as well as local food availability and access.
  - Meal and snack ideas and preparation tips, creating a balanced plate
  - Review of common sources of cross-contamination at home, dining out, and in the grocery store (i.e. cooking equipment and surfaces, shared sponges, shared condiments, bulk bins, deli slicers, salad bars); review of high-risk foods and situations.
  - Resources provided
    - Sample menu of meal, snack, and beverage ideas (**Box 1**)
    - List of "allowed foods" (**Table 2**)
    - Groetch's "Cooking without Common Allergens"<sup>68</sup>
    - FARE "Tips for Avoiding Your Allergen"<sup>69</sup>
    - Computer and phone resources available (Pinterest board, [Yummly.com](https://www.yummly.com) and phone applications)
    - Cookbook recommendations

#### Follow-up nutrition reassessment during food reintroduction (telephone visit, 30 minutes)

- Assess how the patient feels (i.e. their energy, weight maintenance, how they are dealing with life on the diet, any questions and/or concerns)
- Screening for any potential deficiencies and diet recall
- Review of food reintroduction
- Recommend eating the challenge food daily or every other day, providing examples of what foods to use, and reinforcing checking all nutrition labels and ingredients for other allergens. For example, during soy challenge, a patient could use soymilk, soy yogurt, edamame, tofu, and soy sauce that must be labeled as gluten free, reinforcing that regular soy sauce contains wheat.

#### Box 1

##### Six-food elimination diet sample menu

###### Breakfast

- Gluten-free oatmeal with ½ cup fresh berries, topped with ground flaxseed or chia seeds, rice milk

###### Lunch

- Corn quesadilla or tacos with chicken or black beans, vegan cheese products (soy free)<sup>a</sup> like Daiya Cheddar Style Shreds, salsa, avocado

###### Dinner

- Gluten-free pasta<sup>a</sup> or spaghetti squash with ground turkey/beef or lentils, allowed marinara sauce,<sup>a</sup> broccoli; side salad with homemade or bottled dressing<sup>a</sup>

###### Snack ideas

- Popcorn
- Corn tortilla chips and salsa or guacamole<sup>a</sup>
- Hummus<sup>a</sup> with vegetables (baby carrots, cucumber, bell pepper, broccoli, etc)
- Fruit and small handful pumpkin/sunflower seeds
- Apple or banana with Sunbutter

<sup>a</sup> Read ingredients on all packaged foods for dairy (milk), wheat, egg, soy, fish, and nuts.

<b>Dairy Group</b>	<b>Proteins</b>	<b>Grains and Starches Group</b>	<b>Fats and Oils</b>	<b>Beverages</b>	<b>Fruits and Vegetables</b>
Coconut milk/ yogurt/ice cream	All nonprocessed meats: Beef Chicken	Corn and Rice Chex <sup>a</sup> Corn tortillas <sup>a</sup> Corn flour	Avocado Dairy and soy- free margarine	Coffee (with dairy free creamer) Fruit juice	All fresh fruits and vegetables Processed fruits and vegetables <sup>a</sup>
Flax milk	Lamb	Gluten-free breads/cereals/ baked goods <sup>a</sup>	Oil, any type Seeds	Rice/coconut/flax/hemp milk	
Hemp milk	Pork	Gluten-free crackers <sup>a</sup>	Sunflower seed butter	Soft drinks Tea <sup>a</sup>	
Oat milk (must be from gluten free oats)	Turkey Venison Legumes (other than soybeans)	Gluten-free flour/baking mixes <sup>a</sup>	Vegan mayo (ie, Veganaise)	Water Alcohol: wine, gluten-free beer, plain distilled liquors	
Pea milk	Processed meats <sup>a</sup>	Gluten-free pasta: rice, quinoa, corn, lentil/black bean <sup>a</sup>			
Rice milk/ice cream <sup>a</sup>	Protein powders: rice, hemp, pea, quinoa <sup>a</sup>	Grits Gluten-free oatmeal <sup>a</sup> Popcorn <sup>a</sup> Potato Potato chips <sup>a</sup> Quinoa Rice Rice/popcorn cakes <sup>a</sup> Soba noodles (buckwheat) <sup>a</sup> Tortilla chips <sup>a</sup> Sweet potato			
Vegan cheese products (soy-free) <sup>a</sup>					

<sup>a</sup> Please be careful to read all labels for dairy (milk), wheat, egg, soy (soy oil and soy lecithin is ok), nuts, and fish/shellfish. This eliminates many of the common foods in the typical US diet.

## NOVEL TESTING AND FUTURE DIRECTIONS: MAN VERSUS FOOD

With advancements in refining dietary approaches for EoE, several unanswered questions arise around better identifying food triggers, developing less invasive testing for the reintroduction phases, quantifying how much allergen must be avoided for disease remission, and assessing how much time is required to induce disease activity with food or conversely, to washout an allergen.

Given recent data to support the role of food-specific IgG4 in EoE,<sup>70</sup> a recent novel allergen-specific signature testing approach to identify triggers using lymphocyte proliferation assays and esophageal IgG4 levels demonstrated accuracy rates approaching 53% to 75%, outperforming traditional allergy testing.<sup>71</sup> In this pilot work, histologic, endoscopic, and symptomatic improvements were observed, and on average, only two to three trigger foods were necessary to eliminate. However, the histologic response rate was only 25% among diet-compliant subjects.<sup>71</sup> Another novel approach to identifying food triggers is the esophageal prick test in which allergen extracts are endoscopically injected into the esophageal mucosa.<sup>72</sup> In response to wheat, soy, milk, and other allergens, acute and delayed responses were observed in patients with EoE, but not controls. Based on successfully epicutaneous immunotherapy desensitization for IgE-mediated milk and peanut reactions, a recent pilot study demonstrated histologic response in 47% of milk-induced patients with EoE in a per-protocol analysis.<sup>73</sup> Although these approaches are not ready for clinical use, they highlight the need for personalized approaches to guide and simplify dietary restrictions.

During the food reintroduction phase, serial endoscopy is currently required to identify trigger foods. This comes at the cost of several endoscopies, burdens of time and convenience, and risks associated with sedation. These are all limitations to patient acceptability of the dietary elimination approach. Less invasive alternatives to traditional endoscopy are needed and include unsedated transnasal endoscopy, Cytosponge, and the Esophageal String Test. Unsedated transnasal endoscopy with collection of esophageal biopsies can be easily and safely performed in the outpatient setting, is well-tolerated by adult and pediatric patients, and significantly reduced costs compared with sedated esophagogastroduodenoscopy.<sup>74-79</sup> The novel Cytosponge device is a swallowed capsule with an attached string, which expands into a mesh sponge and collects esophageal epithelial specimens when pulled back through the mouth, was initially developed for Barrett's esophagus screening and has an excellent safety profile.<sup>80,81</sup> The Cytosponge has now been shown to be a safe and accurate method to not only assess histologic activity in EoE, but also in pilot data to direct food reintroduction after 6-food elimination, offering an alternative test for monitoring of EoE.<sup>82,83</sup> Additionally, compared with traditional endoscopy with biopsies, this method was found to be considerably less expensive. The Esophageal String Test (EST) is a similarly ingestible capsule attached to a string, which unravels and absorbs esophageal inflammatory samples when withdrawn. In a prospective, multisite study of pediatric and adult patients with EoE, EST accurately identified active versus inactive disease and eosinophil-associated biomarkers obtained from EST correlated with endoscopic severity scores and peak eosinophil counts.<sup>84</sup> Although these minimally alternatives are not currently available for clinical use, they offer promise for techniques in the near-future to streamline diet therapy.

For many patients electing diet therapy, a commonly asked question is how strictly to avoid food triggers. For celiac disease, absolute adherence to a gluten-free diet is supported as the only treatment and tolerable gluten contamination is recommended to be less than 50 milligram per day.<sup>85,86</sup> These thresholds for EoE food triggers and

the dose responses to food antigens remain unknown, and may be key factors in understanding patient adherence and long-term effectiveness of the elimination diet. Additionally, a 6- to 8-week time interval is currently recommended between food reintroductions, but the time to histologic, symptomatic, and endoscopic recovery is unclear.

## SUMMARY

Diet therapy can be an effective, feasible, and durable means of controlling both the symptoms and eosinophilic inflammation in EoE. As an alternative to pharmacologic therapies, this first-line treatment strategy is ideally directed at the allergic basis of EoE by avoiding food antigen triggers; it is a “man versus food” approach. The elemental diet devoid of food allergens yields the best response, but a formula-based diet without solid foods and prolonged food reintroduction can be unpalatable and onerous. In contrast to an allergen-free diet, a targeted elimination approach is limited by poor predictive values of allergy testing to identify EoE food triggers. As a result, allergy testing is not recommended to guide EoE diet therapy in children or adults. The empiric elimination diet involving removal of the most common food triggers and systemic reintroduction is a more acceptable and recommended approach to identifying which foods should be avoided to maintain long-term disease control. However, implementation of the diet is often faced with challenges such as financial cost, inconvenience, patient adherence, cross-contamination, quality of life, and access to resources including nutritional support and endoscopic procedures. Success on diet therapy and long-term adherence relies not only on patient motivation, but can be augmented by partnering with a dietitian who can provide education, feedback, and personalized nutritional treatment plans. Acknowledging these potential barriers and patient preferences, pharmacologic treatments are also reasonable options to maintain disease control in patients who do not respond to dietary restriction, need respite from food avoidance, or struggle with diet adherence. Future directions for EoE dietary therapy include the use of minimally invasive diagnostic tools to simplify food reintroduction and optimizing testing to identify individualized food triggers.

## CLINICS CARE POINTS

- Diet therapy is effective at inducing and maintaining disease remission and is an alternative to pharmacologic therapies.
- Empiric elimination and elemental diets are effective in 43-91% of patients with eosinophilic esophagitis and offers advantages over allergy-test targeted diets.
- The six-food elimination diet meets USDA dietary guidelines for adults.
- Patient-level barriers to the effectiveness of diet therapy include compliance to a restrictive diet, contamination, and education.
- Identifying strategies to maximize patient quality of life and adherence are crucial to successful implementation of diet therapy.

## DISCLOSURE

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