

NARRATIVE REVIEW

Charles J. Kahi, Section Editor

Development of a Practical Guide to Implement and Monitor Diet Therapy for Eosinophilic Esophagitis



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Dietary therapy for short- and long-term management of eosinophilic esophagitis is an effective yet poorly understood and underutilized treatment strategy. Despite several prospective trials demonstrating the efficacy of dietary therapies, successful clinical implementation is hampered by the need for a multidisciplinary approach including dietitian support and provider expertise. The availability of these resources is not readily available to most gastroenterologists. Without standardized guidance on starting or completing the diet for gastrointestinal providers and/or consulting dietitians, provider attitudes toward dietary therapy vary greatly depending on familiarity and knowledge gaps in using diet therapy. This review aims to summarize evidence in support of dietary therapy in eosinophilic esophagitis while providing guidance on initiation and implementation of dietary therapy for providers.

Keywords: Elimination Diet; Food Reintroduction; Eosinophil; Esophagus; Nutrition; Food Allergen.

Eosinophilic esophagitis (EoE) is a chronic inflammatory immune-mediated disease affecting both children and adults, characterized by symptoms of esophageal dysfunction, eosinophilia, and fibrosis of the esophagus. A diagnosis of EoE is made based on symptoms such as dysphagia, food bolus obstruction, and less commonly heartburn, globus, or poor feeding; endoscopic mucosal findings of longitudinal furrows, rings, and strictures; and the presence of esophageal eosinophilia (>15 eosinophils per high-power field [eos/hpf]).^{1–3} This eosinophil-predominant inflammation characteristic of EoE is driven and precipitated by food antigens as affirmed by effective treatment of the disease with diet elimination of specific food allergens.^{4–16}

Current first-line effective treatments aimed at targeting inflammation and preventing fibrostenotic complications such as esophageal strictures and food

impactions include food elimination diets and medications such as proton pump inhibitors, topical corticosteroids (TCSs), and the recently approved anti-interleukin-4 receptor biologic, dupilumab.^{17–19} Medications offer short response time and relative ease of use, but out-of-pocket payments can incur high costs for patients and require inconvenient and nonstandard preparations. Elimination diets offer a nonpharmacologic alternative to disease control, and studies to date demonstrate efficacy similar to that of medications, but require adherence to a strict diet and frequent endoscopies to identify food triggers. Studies to date show that both diet and medications are effective in inducing and maintaining long-term disease remission, reducing the risk of food impactions, and improving health-related quality of life.^{20–24} As such, both are recommended as first-line treatments for EoE.² To date, there are no comparative efficacy studies between diet and pharmacologic treatments.²⁵

Diet therapy can be burdensome for patients to navigate and challenging for clinicians to implement. Consequences of poorly executed diet therapies include overly restrictive food elimination, compromised nutrition or micronutrient deficiency, lack of patient compliance or inadvertent exposures to food antigens, excess costs, “wasted” endoscopic evaluations, misinterpreting refractory disease from nonadherence, and ultimately persistent disease.²⁶ Success with diet therapy can be

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Abbreviations used in this paper: 1FED, 1-food elimination diet; 2FED, 2-food elimination diet; EoE, eosinophilic esophagitis; eos/hpf, eosinophils per high-power field; FFED, 4-food elimination diet; SFED, 6-food elimination diet; TCS, topical corticosteroid.

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augmented by partnering with a dietitian, but access to this clinical resource is not universal and diet education often falls to the clinician.^{27,28} To date, no standardized dietary resources for EoE exist. Our aim is to equip providers caring for EoE patients with evidence-based and practical knowledge to support patients in starting and sustaining an elimination diet for EoE.

Rationale

The role of food allergens in the pathogenesis of EoE was first demonstrated in a landmark study of children with EoE demonstrating clinical and histologic remission on a hypoallergenic amino acid-based elemental formula.²⁹ Since then, several prospective studies have shown a high rate of disease remission on elemental formula among children and adults. Challenges, however, include poor palatability, high financial cost, lack of insurance coverage, and arduous food reintroduction requiring several endoscopies, limiting the uptake of this strategy. In contrast to this highly restrictive approach, empiric elimination diets aimed at removing the most common food triggers are now the favored dietary strategy. Major challenges to the implementation of diet therapy include the need to avoid common foods such as animal milk or wheat and the lack of accurate noninvasive testing to identify inciting food antigens. Although diets guided by allergy testing (eg, skin prick, atopy patch, serum specific IgE), were once considered as a potentially practical approach to identifying EoE food triggers, findings from studies of children and adults with EoE show poor concordance between allergy testing and true trigger foods, thus suggesting that conventional allergy testing is unreliable to identify EoE food triggers.³⁰⁻³³ Furthermore, suspected triggers of inflammation identified through these methods may be detrimental if patients are prescribed overly restrictive diets based on testing. While novel tests are under development to identify food triggers, these are still considered experimental and not available for use in routine practice.³⁴⁻³⁶

Why Care About Dietary Therapy For EoE?

Despite the perceived challenges of dietary therapy for EoE, this approach is increasing in popularity due to patient preference for natural approaches, the use of less restrictive diets, and avoidance of pharmacologic therapies. Patients with EoE report high acceptance of diets and would recommend the diet to others.³⁷ They also value shared decision making around treatment choices for EoE and struggle with providers who lacked disease-related knowledge or did not support diet treatment as an acceptable therapeutic choice.^{38,39} Conversely, prior studies show that physicians prefer to use medications over diet for EoE, view diet as less effective, lack access

to dietitian support, and falsely perceive that patients are not interested in or unable to adhere to food elimination.^{27,40-43}

While pharmacologic therapies offer relative ease of use and are generally well tolerated, short-term side effects of TCSs include oropharyngeal and esophageal *Candida* infections, and there may also be potential and unquantified long-term adverse effects (eg, adrenal suppression) from chronic TCS and proton pump inhibitor use.⁴⁴⁻⁴⁶ Although the safety profile of dupilumab is favorable, known side effects include injection-site reaction, ocular complications of conjunctivitis and ulcerative keratitis, joint pain, and oral herpes.^{17,47-49}

The cost of off-label topical corticosteroids can be prohibitively expensive, as a 6-week course of budesonide respules 1 mg twice daily is estimated to cost \$1613-\$1723, and in a recent cost utility analysis, the median cost was \$2316 per quarter.^{50,51} Compounded budesonide suspensions may offer more affordable options, but downsides include variations in formulation, pharmacy practice patterns, and insurance coverage.⁵²⁻⁵⁴ Cost simulations show that 6-food elimination diet (SFED) is less expensive and more cost-effective than topical budesonide and fluticasone.⁵⁵ Although the recent Food and Drug Administration-approval of dupilumab heralds an era of new treatment possibility for EoE, it remains to be seen if insurance coverage for this high-cost biologic therapy will allow patients long-term maintenance care.

Overview Of The EoE Dietary Approach

The overarching goal of dietary therapy is to maintain disease remission by avoiding specific foods that trigger the T helper cell type 2 response in the esophageal epithelium. This process to identify food triggers includes the following phases: (1) the **elimination phase**, which involves removing a set of foods to first induce disease remission (defined by at least 6 biopsies with significant improvement in eosinophilia, ideally <15 eos/hpf, symptom improvement, improved endoscopic findings); (2) the **reintroduction phase**, which involves systematically reintroducing food allergen groups in order to isolate EoE food triggers that precipitate active disease; and (3) the **maintenance phase**, which involves long-term avoidance of the identified food triggers (Figure 1). As this process involves strict avoidance of 1 or more foods, then careful reintroduction of excluded food allergen groups, adequate patient education, and partnering with a dietitian is essential to increase success in all phases of the diet and long-term adherence.

Because symptoms are often discordant with underlying disease activity, symptoms alone should not be used to make decisions about treatment changes.⁵⁶ Relying on symptoms in isolation to guide food elimination or reintroduction is insufficient and can result in false identification of food triggers and unnecessarily

prolonged dietary restriction. Patients should be warned that their trigger foods are not necessarily the foods that cause immediate symptoms related to obstruction (eg, commonly meats, bread, sticky textures). Endoscopy with biopsy is the gold standard for monitoring response to therapy and is recommended at least 6–8 weeks after a change in therapy, including elimination and reintroduction phases to identify of food triggers.⁵⁷ Tracking progress through each phase of the diet and responses to each food can be helpful, particularly in the case of several identified food triggers or more restrictive diets ([Supplementary Material](#)).

Choosing A Dietary Strategy

Initial standard empiric diet strategies include the SFED, 4-food elimination diet (4FED), 2-food elimination diet (2FED), and 1-food elimination diet (1FED). The most well studied and prototypic of these is the SFED—avoidance of all animal milk products, wheat, soy, eggs, nuts/tree nuts, and seafood (finfish and shellfish)—yielding pooled response rates of ~70% in both children and adults.^{5,7,9} Targeting the more common EoE trigger foods, the less restrictive options of the 4FED (avoidance of animal milk, wheat, soy, eggs), 2FED (animal milk and wheat), or 1FED (animal milk only) offer less food avoidance, abbreviated reintroduction phases, and fewer endoscopies to identify potential triggers.^{10,12,14,15} However, the trade-off is lower response rates ([Table 1](#)). In contrast to the traditional top-down elimination approaches, a step-up strategy beginning with less restrictive diets (1FED or 2FED) and further restricting the diet to the 4FED or SFED if there is nonresponse

allows patients to avoid the most common triggers first and potentially fewer number of endoscopies to identify the triggers ([Figure 2](#)).⁵⁸ The most identified food triggers for EoE are animal milk (up to 90%) and wheat (up to 75%), and up to half of patients who undergo dietary therapy will have more than 1 dietary trigger.^{58,62} In a recent study of adult patients undergoing dietary therapy with the SFED, 69% of patients had only 1 food trigger identified, making this a reasonable option for long-term therapy.⁵⁹

To date, there are no clinical guidelines or recommendations supporting 1 ideal dietary approach for EoE. Key considerations in diet selection are patient preferences and lifestyle, and provider resources to support varying levels of dietary challenges. More restrictive diets in which multiple common food groups are avoided (eg, SFED) not only are more challenging for patients, but also require providers to be familiar with how to restrict, reintroduce specific foods without contamination, and monitor responses to each phase of the diet. Guided by available evidence-based knowledge, providers ought to weigh the advantages and disadvantages of various dietary strategies with patients ([Table 1](#)).

Evaluating Patients For Dietary Therapy

Many patient-level factors must be assessed when considering candidates for EoE dietary therapy, such as patient motivation, preferences and values, age or stage of life, lifestyle, work and living situation, willingness for frequent endoscopies, and possibly finances and insurance coverage for several endoscopies and dietitian costs ([Table 2](#)). Screening for cost or adherence barriers to

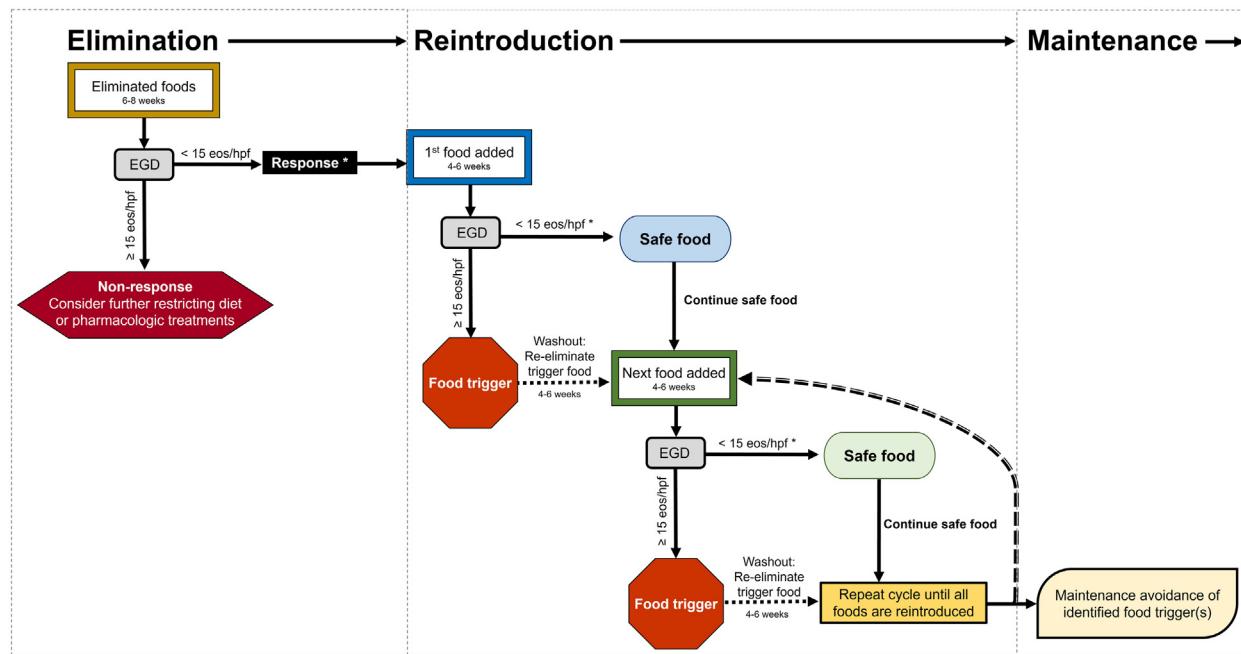


Figure 1. Overall dietary strategy. *Response defined by reduced esophageal eosinophilia <15 eos/hpf, provided endoscopic and symptom improvement is also noted. EGD, esophagogastroduodenoscopy.

Table 1. Summary of Empiric Elimination Diet Strategies

Diet	Eliminated Foods ^a	Pooled Response Rates (%) ^{11,12,14–16,58–61}	Pros	Cons
6-food elimination	Animal milk Wheat Egg Soy Nuts/tree nuts Fish/shellfish	40–73	-Most well studied of the empiric elimination diets -Highest histologic remission rate for empiric elimination diets	-Most restrictive of the empiric elimination diets -High number of endoscopies -Cost -Adherence
4-food elimination	Animal milk Wheat Egg Soy	41–60	-Less restrictive -Greater diet variety -Shortened diagnostic process	-Possible lower remission rate -Cost -Adherence
2-food elimination	Animal milk Wheat	43 ^b	-Even less restrictive -Avoids unnecessary restriction -Shortened diagnostic process -Impact on quality of life ^c	-Possible lower remission rate -Impact on quality of life ^c
1-food elimination	Animal milk	34–65	-Least restrictive diet -Avoids unnecessary restrictions -Shortened diagnostic process -Less endoscopies -Impact on quality of life ^c	-Possible lower remission rate -Impact on quality of life ^c

^aCaveat of systematic reintroduction of foods to identify specific triggers to follow.

^bData from Molina-Infante et al.⁵⁸

^cQuality of life may be patient dependent.

implementing the diet, taking an inventory of the patient's diet history, and assessment of current nutritional status are important in this decision.⁶³ In addition to offering diet as an effective and viable alternative to medication, one must work with the patient to weigh these factors in choosing a therapy plan that is concordant with patient preferences and successful. Although not addressed in detail here, particular care and involvement with a dietitian is necessary for pediatric patients on dietary therapy given specific considerations for growth, development, feeding ability and screening for feeding aversion disorders, and parent and family preferences.

Elimination

As a hallmark of EoE dietary therapy, an empiric elimination approach involves dietary avoidance of 1 or more common food allergens without prior allergy-based testing.⁶⁴ After selection of the planned diet, patients should be educated on how to avoid specific food allergens (*Supplementary Material*). These skills include nutrition label reading to avoid contamination, cross-contact, and accidental ingestion. Because the threshold level of an EoE food trigger is unknown, a strict avoidance of the food allergen group and all sources of cross-contamination is recommended during the initial phases of diet to clearly identify the specific EoE triggers. A wheat-free diet should also exclude gluten-containing grains (eg, oats, barley, rye) due to risk of cross-contamination.⁶⁵ Practical tips such as navigating the

supermarket, sharing sample menus, and ingredient substitutions can optimize patients' experience and adherence during this more restrictive phase (*Supplementary Material*).⁶⁶

As the process of an EoE food trigger causing active disease is not immediate, patients are recommended to remain on the elimination phase for at least 6–8 weeks before endoscopy is performed to assess the response to therapy. Once disease remission is attained in a patient eliminating more than 1 food, reintroduction of foods can begin under physician guidance to identify specific trigger foods. Providers should be aware that some patients may require prolonged elimination to achieve disease remission and benefit from an extended course of dietary elimination (at least 12 weeks) if incomplete response (ie, not yet full response but decreased eosinophilia, improved symptoms, and endoscopic findings) is observed or dietary contamination is suspected after the initial 6- to 8-week assessment.^{59,67}

Addressing Nonresponse

The most common reasons for nonresponse to the elimination phase include purposeful or inadvertent dietary nonadherence, cross-contamination, and incorrect or inadequate removal of potential food triggers. If individuals are unable to attain remission with the initial elimination, taking a detailed history to assess if contamination or adherence should be the first step.

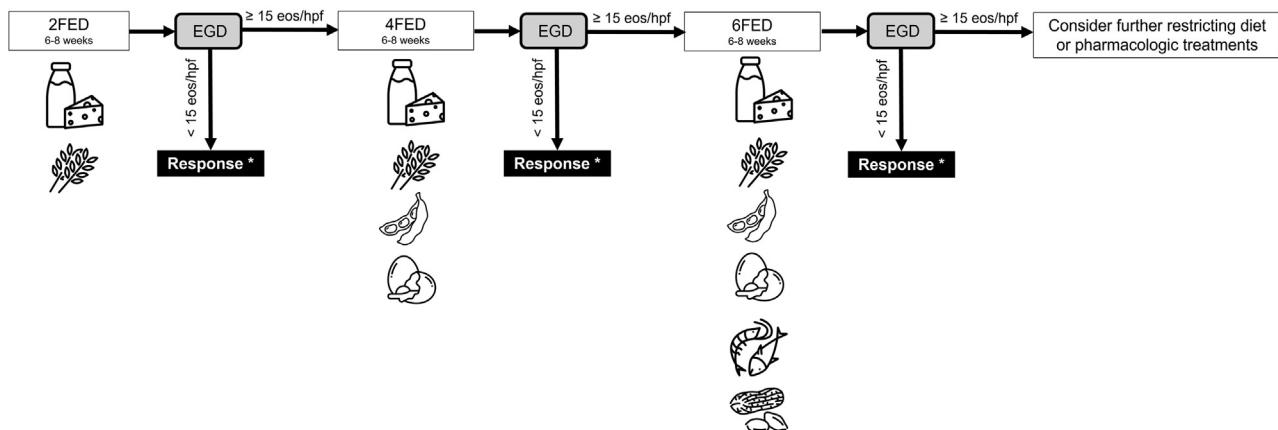


Figure 2. Step-up dietary strategy. *Response defined by reduced esophageal eosinophilia <15 eos/hpf, provided endoscopic and symptom improvement is also noted. If response is attained, then pursue reintroduction to further delineate food triggers.

There are also data to suggest that the presence of aeroallergen disease may attenuate the response to therapy.^{68–70} As a result, working with an allergist to evaluate the potential role of aeroallergens, seasonality, and environmental allergens can be helpful. If no contamination or nonadherence are identified, patients should be presented with an opportunity to remove further food triggers if they started on a less restrictive diet (eg, further restrict to the SFED if started on the 4FED, or restrict to the 4FED from the 2FED) or prolong the elimination phase for an additional 6–8 weeks before again assessing response. In a recent study of adults undergoing the SFED, 27% had increased response with a repeated attempt at diet elimination, highlighting this option for motivated patients.⁵⁹ This and any decisions to engage in restrictive diets beyond the SFED (ie, to include corn, legumes, or beef) ought to involve continued careful shared decision making between the patient and clinician, and dietitian if available.

Reintroduction

Long-term avoidance of several (or all) foods is not the goal and in fact, maintaining a highly restrictive diet

Table 2. Considerations in Patient Selection

Considering a Patient for EoE Dietary Therapy

- High patient desire and motivation to undergo dietary therapy and/or avoid medications
- Patient personal preferences and values
- Patient's age, life stage, living situation, lifestyle (including travel, dining-out habits) to enable ability to shop for and adhere to a strict diet
- Patient's nutritional status and any self-restrictive behaviors toward foods
- Patient's willingness to have and travel for frequent endoscopies
- Patient's finances and insurance coverage (if high deductibles for procedures)

misses the point of dietary therapy to identify and avoid specific food triggers for long-term disease remission. While patients vary in the number of triggers, most have between 1 and 3 food triggers. The reintroduction phases involve adding back 1 or 2 individual food groups while still avoiding the others, and monitoring response with endoscopy and biopsies to determine if each is a trigger or safe food. The reintroduction phase cannot begin until disease remission is attained with empiric elimination (confirmed with endoscopy and biopsies), as the identification of a food as a trigger or safe relies on eliciting recurrent disease activity or sustained disease remission, respectively. After the elimination, if a reintroduced food results in sustained disease remission, it is deemed a safe food and can be consumed. Conversely, if the reintroduced food results in recurrent disease activity, it is a trigger food and must be avoided. Because symptoms alone are an unreliable metric of underlying disease activity, endoscopy with biopsies is required to monitor response 6–8 weeks after a change is made to determine if the reintroduced food is safe vs if the reintroduced food is a trigger. While single-food reintroduction (ie, adding back 1 food group at a time) most accurately determines if individual foods groups are triggers, an abbreviated approach by adding back less likely foods together can be attempted as well (ie, reintroducing nuts and fish together). However, the most common triggers (animal milk, wheat, egg, and soy) may be introduced individually.

During each food reintroduction phase, patients should be advised to consume at least 1 serving of the challenge food per day for at least 4–6 weeks prior to monitoring response with endoscopy and biopsy while still avoiding the other food groups ([Supplementary Material](#)). Consuming inadequate amounts of the challenge food could result in false negatives in identifying a food trigger.

The order in which to reintroduce food groups generally begins with the least likely food triggers ([Figure 3](#)).⁷¹ As such, standard practice is to reintroduce in the following order: seafoods → nuts → soy → egg → wheat → milk.

Table 3. Checklist for a Dietary Approach to EoE

Providers should perform an initial office visit to understand the patient's symptoms, current diet, past experiences with treatments, concerns, values, and preferences for disease management.
Given the various dietary strategies and elimination options, providers should individualize the elimination diet to meet the patients' needs.
If available, providers should identify a dietitian or nutritionist to partner with.
Potential barriers to diet adherence should be explored before starting the diet (eg, high deductible for endoscopies, inability to prepare meals).
All patients should be counseled about time commitment and number of endoscopies to anticipate during dietary therapy, with the ultimate goal of identifying trigger vs safe foods.
All patients on dietary therapy should have endoscopy with biopsies to monitor responses to the elimination and individual food reintroduction phases.
Current restrictive dieting behaviors or previous history of eating disorder should be considered carefully before embarking on diet elimination. In patients already on prolonged and overly restrictive diets, the benefit of dietary therapy should be weighed against the risk of malnutrition. A history of eating disorder does not prevent using dietary therapy but may influence the level of dietary restriction considered for treatment.

EoE, eosinophilic esophagitis.

As animal milk and wheat are the most common EoE food triggers, these are recommended to be last (not first) foods to be reintroduced (unless there is a strong patient preference otherwise). During the reintroduction phases, if a food elicits disease recurrence, this is deemed a trigger food and the patient should undergo a washout period in which the trigger food is avoided for 4–6 weeks prior to reintroducing the next food group. If one food trigger is identified, the remaining foods should still be systematically reintroduced because up to 31% of patients may have more than 1 food trigger.^{58,59}

The ultimate duration of the reintroduction phase is determined by the degree of initial dietary restriction (ie, how many foods initially eliminated) and number of food groups to add back. For example, beginning with a more restrictive diet will require prolonged time for individual food reintroduction and a greater number of endoscopies to identify each as a safe or trigger food. In contrast, starting with a less restrictive diet (eg, 2FED), fewer foods will need to be reintroduced if initially responsive, fewer number of endoscopies is required to identify food triggers, and less time is spent in the reintroduction phase.

Maintenance

Once the specific food triggers are identified, the long-term goal of sustained disease control involves maintenance avoidance of those trigger foods. As EoE is a chronic disease, after being in remission disease activity can quickly recur if food avoidance is discontinued.

Anticipating Challenges

Although many patients may desire a dietary approach to EoE, making it a tenable and positive experience can be as challenging when deciding to start the diet. As the process to eliminate and reintroduce foods is an extended process which will take several months, anticipating and providing education around social events and dining out ([Supplementary Material](#)) or allowing diet “holidays” can make the process less daunting. There may be times when a patient needs a break or diet holiday to temporarily lift their diet restrictions (eg, particularly around end-of-the-year holidays, vacations, life events), then resume avoiding their food triggers when ready. In most cases, care should be

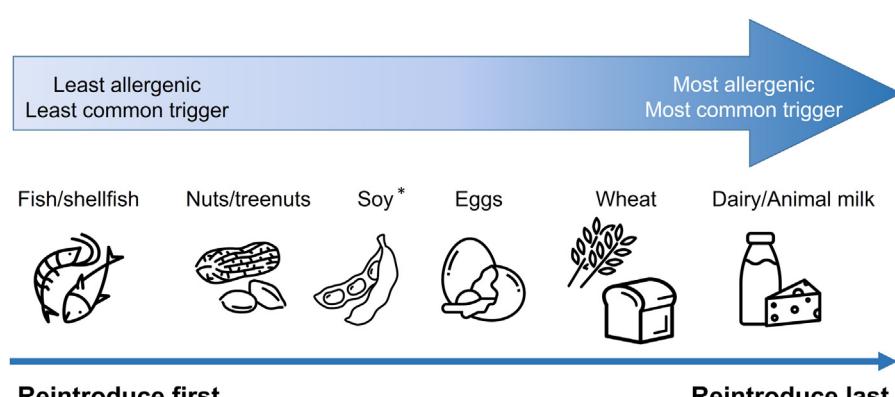


Figure 3. Proposed reintroduction order. *Reintroduction order of soy and egg may be interchangeable. Reintroduction order of food groups can be modified based on preference, but this proposed order yields the quickest and most efficient reintroduction process.

taken to plan the elimination and reintroduction schedule in advance to avoid taking several breaks during a drawn out and burdensome diet. If a diet holiday is necessary during the food reintroduction phases, endoscopy must be scheduled 6–8 weeks out from when they resume the diet at the stage where they left off. Patients known to be responsive to both diet therapy (with identified food triggers) and medications may also elect to switch between treatment modalities depending on life events and situation. Thus, even if a patient chooses diet therapy, identifying an effective pharmacologic therapy may better guarantee continued disease remission during diet holidays, and may improve quality of life and long-term adherence to their diet.

Though many patients are motivated to pursue non-pharmacologic treatments for EoE, providers must take caution to avoid progressively restrictive diets in the face of diet nonresponse, requiring or leaving patients on strict elimination indefinitely, and assess for avoidant restrictive food intake disorder.^{72,73} Similarly, providers should use discretion when considering dietary therapy in patients with known history of eating disorders and only in collaboration with a dietitian and approval from their treating therapist.

Partnering With A Dietitian

As dietitian support and access is not a universal resource for all clinicians, we encourage providers to reach out to nutrition experts with specialized interests in dietary therapies for eosinophilic gastrointestinal diseases. Additional online resources and directories of dietetic providers with expertise in these areas can be found in the Supplementary Material.

Conclusion

Dietary therapy is an effective first-line treatment for EoE and offers patients a nonpharmacologic alternative to control disease activity. Empiric elimination diets are the favored approach to diet therapy and significant progress has been made to identify food triggers. Dietary therapy can be effectively implemented with dietary education, resources for patients, and close patient-provider communication. Supplementary resources provided in this review can be used to provide this dietary education. With the advent of new therapies for EoE and evolving recommendations for treatment, recognizing and balancing patient preferences for nonpharmacologic approaches and clinical resources are crucial for delivering high-quality patient centered EoE care.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <http://doi.org/10.1016/j.cgh.2023.03.006>.

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Conflicts of Interest

The authors disclose no conflicts.

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