Dietary Treatment of Eosinophilic Esophagitis in Children

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Key Words

Six-food elimination diet · Elemental diet · Patch testing

Abstract

Eosinophilic esophagitis (EoE) is a chronic inflammatory disorder of the esophagus that, in a genetically susceptible host, is triggered by a food antigen. Emerging evidence supports impaired epithelia barrier function as the key initial event in the development of EoE and other allergic diseases. Symptom resolution, histologic remission, and prevention of both disease and treatment-related complications are the goals of treatment. Successful dietary treatments include elemental and elimination diets, both empiric and allergy test directed. These treatments are dietary approaches to inducing clinical and histologic remission. Dietary therapy with an exclusive elemental diet offers the best response with a remission rate of more than 96%. Empiric elimination diets and allergy-directed diets offer similar response with remission induced in 3 of 4 subjects (75%). Cow's milk, wheat, egg and soy are the four common food antigens most likely to induce esophageal inflammation.

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Introduction

Eosinophilic esophagitis (EoE) is an antigen/immune-mediated chronic inflammatory disorder that, in a genetically susceptible individual, is triggered by food antigens.

EoE in children was first described in 1995 in a case study demonstrating reversal of clinical symptoms and esophageal eosinophilic inflammation with replacement of all food antigens with an exclusive amino acid-based elemental diet [1]. Specific food antigens including cow's milk, soy, wheat, egg and peanuts were shown as potential proteins that induced the esophageal inflammation. These seminal observations from that study have become the basis of the different dietary approaches currently offered to treat EoE.

As is true for the treatment of most other chronic disorders, the goals of treatment in EoE include: (1) resolution of clinical symptoms, (2) maintenance of remission, (3) prevention of complications such as fibrosis and strictures by maintaining histologic remission, (4) prevention of iatrogenic treatment-related adverse reactions such as nutritional deficiencies in dietary treatment, and (5) maintenance of quality of life.

The dietary approach is based on the hypothesis that food antigens trigger eosinophilic inflammation, and both clinical and histologic remission can be induced by identifying and excluding the causative food antigens. Eliminating causative food antigens targets the cause, thus eliminating and continuously avoiding the food antigen and thereby inducing long-term remission. There are no prospective studies assessing the efficacy of the different dietary approaches in children. The current recommendation for treatment of EoE with diet are based on a number of retrospective and observational studies [2–

Table 1. Dietary introduction approach to food reintroduction in EoE

Start (least allergenic)		→ End (most allergenic)	
A	B	C	D
Vegetables (nonlegume) Carrots, squash (all types), sweet potatoes, white potatoes, string beans, broccoli, lettuce, beets, asparagus, cauliflower, brussel sprouts	Citrus fruits Oranges, grapefruits, lemons, limes Tropical fruits Bananas, kiwis, pineapples, mangos, papayas, guavas, avocados Melons Honeydew, cantaloupe, watermelon	Legumes Lima beans, chickpeas, white/black/red beans Grains Oats, barley, rye, other grains Meat ¹ Lamb, chicken, turkey, pork	Fish/shellfish Corn Peas Peanuts Wheat Beef Soy Eggs Milk
Fruit (noncitrus, nontropical) Apples, pears, peaches, plums, apricots, nectarines, grapes, raisins	Berries Strawberries, blueberries, raspberries, cherries, cranberries		
Vegetables Tomatoes, celery, cucumbers, onions, garlic, any other vegetables	Grains Rice, millet, quinoa		

Modified with permission from Markowitz et al. [4]. ¹ Progress from well-cooked to rarer.

7]. The available dietary approaches include: (1) an elemental diet with an amino acid-based complete liquid formulation [1, 2, 4], (2) a directed elimination diet based on the results of allergy testing [5], and (3) an empiric or nondirected elimination diet where a number of common food antigens are initially and temporarily excluded from the diet [3]. The type of treatment selected should be tailored to the needs of the patient. The selection will depend on the age of the child, the presence of comorbid malnutrition and feeding aversion, and the comfort and acceptance of the elimination diet by the family. Outcomes of all the different dietary approaches are summarized in figure 1.

Elemental Diet

In a cohort of 10 children with gastroesophageal reflux disease-like symptoms that had been resistant to prior acid suppression, a crystalline amino-acid based (exclusive) elemental formula in lieu of a regular diet induced clinical and histologic remission. Subsequent controlled reintroduction of solid foods resulted in recurrence of gastrointestinal symptoms specific to individual foods. A clear link between food allergy and esophageal injury was thus established in these patients [1]. Since this seminal publication by Kelly et al. [1], two series of 172 and 25 cases reported a remission rate of 96 and 88%, respectively, in children treated with an elemental diet without any reported complications [2–4]. The likelihood of

Fig. 1. Spectrum of different dietary treatments by response.

achieving mucosal healing is higher with this modality than other dietary or pharmacologic treatment with corticosteroids. The added advantage is the much lower residual eosinophil counts. The disadvantage of this approach is compliance secondary to the poor taste. This is also the reason why many of these children require either nasogastric or gastrostomy tubes to deliver adequate nutrients. Limiting a child to an exclusive elemental diet may also restrict the child's participation in social activities, since many childhood activities involve food, which can lead to impaired quality of life. The elemental formulas are expensive and this can potentially place significant financial and social burden on the families. There may also be additional costs related to tubes, pumps, bags, and other supplies.

Following demonstration of histologic remission 4–6 weeks after the exclusive elemental diet, food reintroduction is initiated beginning with the least allergenic foods from vegetable or fruit groups, then single foods are introduced every 5–7 days, and followed by single foods from the most allergic food group which includes cow's

milk, soy, wheat, egg, beef, and corn. The reintroductions are outlined by Markowitz et al. [4] as shown in table 1. Following successful reintroduction of all foods in one food group, endoscopic esophageal biopsies are performed to demonstrate continuing remission before introducing the next single food from the next food group. In this process, if symptoms are elicited with an ingested food, then the symptom-inducing food is excluded from the diet and the next food in that group is introduced once the symptoms have resolved.

Directed Elimination Diets

Elimination diets based only on the results of RAST and/or a skin prick test (SPT) have failed to demonstrate clinical and histologic remission [7–9]. In a prospective study in adults treated with empiric elimination diet who also underwent SPT, the predictive value of SPT for causal foods was only 13% in subjects [6]. RAST testing and SPT alone or together fail to correctly identify foods causing esophageal inflammation in most patients. However, an elimination diet in children based on the combined results of SPT and atopic patch testing (APT) resulted in clinical and histologic remission in 72% [5]. Patients in this series were tested on a total of 23 foods in five food groups that included meats (chicken, turkey, beef, and pork), vegetables (peas, string beans, squash, sweet potatoes, potatoes, and carrots), fruits (apples, pears, and peaches), grains (wheat, rice, rye, oats, barley, and corn) and a final group which included cow's milk, soy, eggs, and peanuts. The foods most frequently identified in patients who underwent a combination of APT and SPT were milk, soy, wheat, chicken, and beef. Other investigators utilizing patch testing in children have been unable to reproduce the high response rates elicited by Spergel et al. [19, 20]. Possible reasons include lack of validation between EoE and control population, and lack of standardization of whether fresh or preserved food extracts are used for testing. For all of these reasons, patch testing remains primarily a research tool [10].

Empiric Elimination Diets

The empiric or nondirected elimination diet does not require allergy testing to determine foods for elimination from the diet, which is the major advantage of this dietary approach over the directed elimination diet. In a study of children treated with a six-food elimination diet

(SFED; i.e. excluding cow's milk protein, wheat, egg, soy, peanut/tree nuts, and fish/shellfish [3]), 26 of 35 children (74%) experienced significant clinical and histologic improvement (esophageal eosinophil count ≤ 10 /high-power field). There was complete mucosal healing with 0–1 eosinophils/high-power field documented in 7 of these 26 children (27%). The histologic response to the elimination diet is shown in figure 2. Two additional studies have recently validated the results of SFED with the histologic response ranging from 50 to 81% [11, 12]. This treatment approach has also been validated in adults with a recent prospective study demonstrating histologic improvement in 72% of patients treated with SFED [6]. In a follow-up study of children achieving histologic remission on SFED, milk was the single most common food and was responsible for triggering eosinophilic esophageal inflammation in 74% of subjects, followed by wheat in 26%, egg in 17%, and soy in 10% [13]. Two additional studies have validated the findings of the initial publication identifying milk, wheat, egg, and soy as the four foods most likely to trigger inflammation in EoE [11, 12].

In the interest of simplification, dietary therapy can be broadly divided into three stages. The first is the remission stage in which multiple foods are concurrently eliminated, as described above, and it is applicable for both elemental and elimination diets. The second stage is the reintroduction stage which is characterized by reintroduction of one of the excluded foods sequentially every 6–8 weeks followed by endoscopy and biopsies in the responders. When there is recurrence of inflammation, the incriminating trigger food is excluded from the diet and the next food is added until all the excluded foods are reintroduced. Ultimately the reintroduction process identifies one or rarely two foods as the cause of esophageal inflammation. The third is the maintenance stage, during which the incriminating food(s) identified during the reintroduction stage is (are) the only food(s) excluded long-term. There are currently no pediatric studies demonstrating the efficacy of long-term continuous elimination of incriminating food antigen(s) maintaining disease remission in children.

The primary advantage of an elimination diet over an exclusive elemental diet is that it allows the intake of a variety of table foods including meats, grains, fruits, vegetables, and legumes compared to a single nutrient source taken orally or via a tube. The major limitation of an empiric elimination diet is the difficulties associated with simultaneously eliminating multiple foods even if for a lim-

Fig. 2. Pre- and posttreatment peak eosinophil counts after SFED (n = 35). Reprinted from original article by Kagalwalla et al. [3].

ited time. There is poor correlation between symptoms and disease activity, and in the absence of noninvasive tests, multiple endoscopies are required to identify recurrence of inflammation, which occurs when the incriminating foods are reintroduced back in the diet of the responders.

Nutritional Assessment

Nutritional assessment of children with EoE prior to initiating an elimination diet improves compliance of the prescribed nutritional therapy. It involves obtaining a detailed nutritional history, including descriptions of the food and supplements being consumed (including brand names of foods), preparation methods, and eating environment. Younger children with vomiting, feeding aversion, and multiple IgE-mediated food allergies may present with malnutrition. The initial assessment may also identify preexisting nutritional deficiencies which can be addressed concurrently when prescribing an elimination diet. Children who are on elimination diets for a prolonged period will need to have their nutritional intake monitored. In addition to anthropometric measurements including weight, height, and BMI, some children, especially those who have a large number of foods excluded, will require biochemical tests including a complete blood count, prealbumin, iron, calcium, and vitamin D levels to monitor for deficiencies [14, 15].

Food Substitutions and Cross-Contamination

The deleterious consequences of eliminating major foods such as milk, soy, wheat or egg from the diet of a growing child are addressed by involvement of a dietitian with understanding and expertise in food substitution. Adequate food substitution of the excluded foods ensures a nutritionally complete diet. This requires knowledge and understanding of the nutrient deficiencies caused by elimination of specific food as well the appropriate substitution for that food as shown in table 2.

Another important aspect of eliminating foods from the diet involves understanding and preventing food cross-contamination. Cross-contamination can transform a naturally occurring antigen-free food into an antigen-containing food. Cross-contamination can occur during processing, preparing, cooking, or serving food. Many processed foods, including fast foods, may be cross-contaminated with one or more foods such as milk, soy, wheat, or nuts. Cross-contamination can also occur during the process of food preparation at home and can be avoided by simple measures such as using different utensils and strict hand washing between cooking different foods.

Reading food labels is a must to ensure that those products are not allowed in the diet. Food labels should be reviewed every time because manufacturing or processing may have changed, and a food that was formerly antigen-free may contain the excluded antigen.

Table 2. Potential nutritional deficiencies

Food	Nutrients	Alternative food sources
Milk	protein, calcium, vitamin D, vitamin A, B ₁₂ , riboflavin, pantothenic acid, potassium	meats, legumes, whole grains, nuts, fortified foods (with B vitamins, calcium, vitamin D)
Egg	protein, vitamin B ₁₂ , pantothenic acid, biotin, selenium	meat, chicken, legumes, whole grains
Soy	protein, iron, zinc, magnesium, thiamin, riboflavin, pyridoxine, folate	meats, allowed grains
Wheat	iron, thiamin, riboflavin, niacin, folic acid	alternative grains that are fortified
Peanut/tree nut	vitamin E, niacin, magnesium, manganese, chromium, folic acid, B ₆ , copper, zinc, selenium, phosphorus, potassium	legumes, whole grains, vegetable oils
Fish/shellfish	vitamin E, B ₆ , niacin, phosphorus, selenium, omega-3 fatty acids	whole grains, meats, soybeans, flaxseed, nuts, oils

Complications

Exclusion of important food elements from a growing child's diet can have disastrous consequences including impaired growth, rickets, and vitamin deficiencies [16–18]. Kwashiorkor from protein-calorie malnutrition has been reported in children with only milk protein exclusion from the diet of toddlers suspected of milk protein allergy [18]. Frequently, it is not only the exclusion of one specific food that results in nutritional deficiency, but also the concurrent exclusion of processed foods that may contain that particular food antigen.

Elimination diets with the emphasis on excluding milk, wheat, soy, and nuts among other foods can also be challenging for children on a vegan diet. Participation of a registered dietitian ensures a calorically adequate diet for growth, provides education on appropriate food substitutions, prevents contamination with excluded food antigens, and is an ongoing resource for families as they learn to adapt to the diet modification.

Conclusion

Dietary treatment is a logical approach to treating EoE. Identification and exclusion of specific food triggers leads to resolution of symptoms and esophageal mucosal healing. Implementation of the various dietary treatments can often be challenging and may be difficult to implement. An elemental diet with complete elimination of all intact food antigens offers the best outcome results as well as the most complete healing; however, the major drawback is excluding all solid foods and the long food reintroduction process which is often frustrating.

The directed and empiric elimination diets that require the elimination of a limited number of foods is more readily acceptable compared to the complete elimination of all intact food proteins from the diet as required by the elemental diet. Although the responses to directed and empiric elimination diets are similar, the directed elimination diet requires the additional step of subjecting the patients to allergy testing without providing added advantage. Furthermore, allergy testing has limitations. SPT alone is ineffective in identifying the trigger foods and APT is not validated, not universally available, and hard to replicate.

Elimination diets are an acceptable modality to treat children with EoE, despite the limitations of requiring multiple endoscopies. The future availability of a minimally or noninvasive test would alleviate the current difficulties with administering dietary management. One size does not fit all when considering different dietary therapies and it is important to remember that success with the dietary approach is primarily contingent on tailoring the specific treatment to the needs of individual patients.

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