ORIGINAL ARTICLES

Effect of Six-Food Elimination Diet on Clinical and Histologic Outcomes in Eosinophilic Esophagitis

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Background & Aims: In children, eosinophilic esophagitis (EE) is predominantly, but not exclusively, a food-hypersensitivity disorder. A crystalline amino acid–based elemental diet (ELED) formula currently remains the most effective nutritional treatment in inducing clinical and histologic remission. However, compliance with an exclusive, poor-tasting liquid formulation is difficult. **Methods:** This retrospective observational study assessed the short-term clinical and histologic responses of 2 cohorts of children with EE evaluated during 2 different time periods: one was treated with the standard 6-food elimination diet (SFED) and the other was treated with ELED. Of the 60 children who met the inclusion criteria and were compliant with the dietary protocol, 35 were treated with a diet excluding cow-milk protein, soy, wheat, egg, peanut, and seafood while allowing all other table foods and 25 were treated exclusively with ELED. Repeat esophageal biopsy specimens were obtained at least 6 weeks later. **Results:** Twenty-six of 35 (74%) in the SFED group and 22 of 25 (88%) in the ELED group achieved significant improvement of esophageal inflammation (≤10 eosinophils/high-power field). The pretreatment and posttreatment peak eosinophil counts for the SFED were 80.2 ± 44.0 and 13.6 ± 23.8 ($P < .0001$) and 58.8 ± 31.9 and 3.7 ± 6.5 ($P < .001$) for the ELED group, respectively. **Conclusions:** SFED treatment was associated with clinical and histologic improvement in EE in an observational study. It offers advantages of better acceptance, cost, and compliance than ELED and should be considered as an option in the initial management of children with EE.

Eosinophilic esophagitis (EE) is a chronic inflammatory disorder characterized by dense eosinophilic infiltration of the esophageal epithelium with gastroesophageal reflux disease–like symptoms resistant to aggressive acid suppression. In 1995, Kelly et al[1] described a cohort of 10 children with esophageal eosinophilia resistant to multiple courses of standard antireflux therapy whose long-term symptoms and biopsy examination results improved once intact protein was removed from their diet and replaced with an amino acid–based formula. Subsequent controlled re-introduction of solid foods resulted in recurrence of gastrointestinal symptoms specific to individual foods. This seminal article established a clear link between food hypersensitivity and esophageal injury in that group of patients. Several descriptive pediatric studies have since established EE as a distinct clinical entity different from severe peptic esophagitis resulting from gastroesophageal reflux disease.[2–9]

Besides elemental diet, the only effective treatment approach for this disorder has been topical and systemic glucocorticosteroids, which induce only temporary clinical and histologic remission.[10–13] After initial induction of remission with corticosteroids long-term maintenance steroid therapy is necessary to maintain remission. Prolonged use of systemic corticosteroids is associated with numerous well-known side effects including adrenal suppression, cataracts, and growth retardation; candidiasis has been reported with topical steroids.[13–15] Other novel therapies for EE include montelukast, a selective D4-receptor antagonist that has shown clinical without corresponding histologic improvement in adults,[16] and mepolizumab, an anti–interleukin-5 monoclonal antibody that has been used to treat hypereosinophilic syndrome and has resulted in resolution of symptoms and reduction of esophageal eosinophilia in a single adult patient with EE.[17] Safety profile and optimal dosing in children are awaited pending phase II trails. In contrast to these therapies, substitution of all intact protein with an exclusive crystalline amino acid–based formula is an effective, if unpalatable, treatment modality that both relieves clinical symptoms and normalizes esophageal histology in EE.[12] This approach has been used more widely because it lacks the potential side effects associated with steroid therapy and it eliminates the underlying source of esophageal injury. However, compliance with elemental therapy can be compromised because of its poor taste.[18] This difficulty is often overcome by using nasogastric or gastrostomy feedings that compound patient discomfort and parental distress. The exclusion of all solid foods coupled with the monotonous same liquid nutrient can lead to frustration and dietary cheating. The child's participation in many social activities can be curtailed because most activities revolve around food.[19]

In an effort to make the dietary approach more palatable, and to overcome the compliance resistance, we explored an alternative dietary approach of eliminating several, but not all, intact food proteins with a 6-food elimination diet (SFED). We specifically excluded milk protein, soy, egg, wheat, peanut/tree

Abbreviations used in this paper: EE, eosinophilic esophagitis; ELED, elemental diet; HPF, high-power field; SFED, 6-food elimination diet.

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nuts, and seafood, which are not only foods that are associated most commonly with food allergies in children, but also those most commonly reported to cause esophageal mucosal injury in children with EE.[20,21] Because the majority of solid foods are allowed we believed this diet would be more acceptable to the patients and their families. If healing occurred on SFED then the number of foods that would need to be re-introduced to determine the offending antigens would be greatly reduced. The primary objective of the present study was to establish that SFED is efficacious in treating children with EE and the secondary objective was to assess the compliance relative to an elemental diet (ELED), which is the most common dietary modality in children.

Materials and Methods

Definition of Eosinophilic Esophagitis

Children and adolescents with chronic gastrointestinal symptoms including vomiting, epigastric abdominal pain, dysphagia, food impaction, failure to thrive, and food aversion who were refractory to proton pump inhibitor therapy (lansprazole, omeprazole) were diagnosed with EE based on 20 or more eosinophils per high-power field (HPF), equivalent to 400× magnification, in the esophageal biopsy specimens with normal gastric and duodenal biopsy specimens. The eosinophil counts were from an area of the esophagus with the highest number of eosinophils for both the initial diagnostic and after intervention therapy and are referred to as the *peak eosinophil count*. Midesophageal and distal esophageal biopsy specimens were required for the initial assessment but patients referred from outside institutions with only distal esophageal biopsy specimens also were included in the study. All biopsy specimens were reviewed by a single board-certified pathologist (H.M.-A.) blinded to the clinical information. Patients treated with swallowed steroids or leukotriene-receptor antagonist were excluded.

Study Design and Participants

This observational study examined 2 cohorts of children with EE seen in the division of Gastroenterology, Hepatology, and Nutrition at Children's Memorial Hospital in Chicago, Illinois. One cohort of 27 children was diagnosed with EE between January 2001 and September 2003 and was treated with ELED consisting of a crystalline amino acid–based formula (Neocate, Neocate EO28, Neocate 1+; SHS International, Liverpool, UK, or Elecare; Ross Pediatrics, Abbott Laboratories, Abbott Park, IL); all solid foods were excluded from the children's diet in this group. Compliance with ELED required administering the formula via nasogastric or feeding gastrostomy tubes.

Between October 2003 and June 2005, a second cohort of 39 children with EE were managed with the SFED, which permitted all solid table foods except cow-milk protein, soy, egg, wheat, peanut/tree nuts, and fish. Processed foods that contained these 6 foods as ingredients also were excluded from the diet. The choice of these 6 foods was based on the list of most common allergenic foods previously reported.[20,21] The duration of this diet was 6 weeks, with systematic expansion of the diet once histologic recovery was shown. A registered dietitian (S.R.) initially instructed and regularly counseled (and responded to telephone and e-mail inquiries) the parent(s)/guardian(s) about the SFED and provided printed lists that clearly identified the foods to be avoided and instructions about carefully reading food labels to avoid cross-contamination. The parent(s)/guardian(s) also were instructed on how to achieve an age-appropriate balanced diet in the face of elimination of several common food stuffs. All patients had their weight monitored after 6 weeks at the time of repeat endoscopy. During the initial evaluation patients' parents were asked open-ended questions about their clinical presentation but at their follow-up posttherapy visit they were questioned specifically if their initial symptom(s) resolved, improved, or did not change.

Outcome Measures

Outcome measures were based on symptomatic and histologic responses to either of the 2 dietary approaches. Histologic outcomes were based on posttreatment esophageal (mid- and distal) peak eosinophil counts in the area of highest density irrespective of the biopsy examination site. They were defined as follows: complete histologic resolution or healing for peak eosinophil count of 0–1 per HPF, significant histologic improvement for peak eosinophil count up to 10 per HPF. Partial response was defined as a peak eosinophil count between 11 and 20 per HPF and treatment failure was defined as a peak eosinophil count greater than 20 per HPF after 6 weeks treatment. Pretreatment and posttreatment symptoms also were reported. The principal outcome measure for improved histologic outcome for the purpose of this study was an esophageal eosinophil count of 10 or less per HPF after dietary therapy with either ELED or SFED. The treatment end point thus was endoscopic biopsy examination after at least 6 weeks after treatment with either dietary modality.

Statistical Methods and Analysis

Paired *t* tests were used to analyze the differences in pretreatment and posttreatment histology and significance was defined as a P value of less than .05. Equivalence testing was used to compare the proportion of patients with significant histologic improvement, as defined by a mucosal eosinophil count of 10 per HPF or less after treatment by ELED and SFED. A 95% confidence interval for the differences in the proportion of patients who improved was calculated. This confidence interval was compared with a range for a nontrivial clinical difference (−10 to +10) to determine equivalence. The data were analyzed by using SAS version 9.1 (SAS Institute, Cary, NC).

Ethics

This study was approved by the institutional review committee at Children's Memorial Hospital in Chicago, Illinois.

Results

Of the 39 children (72% boys) who were managed with SFED, 4 were dropped from the study: 2 for dietary noncompliance and 2 for having more than 6 foods excluded from their diet. Of the 27 children (82% boys) begun on ELED, 2 were dropped from the study for dietary noncompliance. The patient profiles and symptoms of the 2 groups were similar with the exception that the ELED group had more children presenting with failure to thrive and food aversion compared with the SFED group (Tables 1 and 2). Only 7 ingested the ELED and 18

Table 1. Patient Profile

	SFED	ELED
Number of patients	35	25
Mean age, *y*	6.2	6.4
Male sex, n (%)	26 (74)	22 (88)
Ethnicity (white/black/Asian/Latino)	27/4/2/2	16/4/4/1
Atopic, n (%)	20 (57)	14 (56)
Eczema/asthma/rhinitis	12/8/7	11/9/3

NOTE. A total of 60 patients were included in the study.

(72%) required administration via either nasogastric (9) or gastrostomy (9) tube.

The clinical symptom response of patients to the 2 treatments is shown in Table 2. The 5 children with failure to thrive treated with SFED showed a mean weight gain of 1.32 kg (range, .9–2.0 kg) over 6 weeks of treatment. The mean weight gain in children with failure to thrive in the ELED group was 1.03 kg (range, .1–2.1 kg). We were unable to assess the response of food aversion in the ELED group because all 6 were only tube fed.

Pretreatment midesophageal and distal esophageal biopsy specimens were obtained from 51 patients and 9 referred patients had only distal esophageal biopsy specimens. Figures 1 and 2 show the peak individual pretreatment and posttreatment eosinophil counts for all SFED and ELED patients. The peak mucosal eosinophil counts from biopsy specimens at presentation and posttreatment for the ELED group were 58.8 $\pm$ 31.9 and 3.6 $\pm$ 6.5 ($P < .001$), respectively, and 80.2 $\pm$ 44.0 and 13.6 $\pm$ 23.8 ($P < .0001$), respectively, for the SFED group. Complete mucosal healing was seen in 10 of 35 (29%) in the SFED group and in 14 of 25 (56%) in the ELED group. The post-treatment biopsy examination mucosal eosinophil counts met the criteria for significant histologic improvement ($\leq$10/HPF) in 74% and 88% of children in the SFED and ELED groups, respectively, and are shown in Table 3. Therefore, the majority of children in both groups met the criteria for significant histologic improvement in response to dietary therapy.

Of the 6 children who failed SFED, 1 had subsequent significant histologic improvement in esophageal eosinophilia when milk protein cross-contamination in processed food was eliminated. Of the SFED failures treated with ELED, 3 had significant and 1 had partial histologic improvement. One patient refused ELED or corticosteroid treatment. The only patient in the ELED group who did not respond to treatment also serially failed topical and systemic corticosteroid treatment and was classified as nonallergic EE.

Discussion

In this study, the SFED, excluding cow-milk protein, soy, egg, wheat, peanut/tree nuts, and fish induced improvement in clinical symptoms and significantly reduced esophageal mucosal eosinophilia in a majority of children with EE. The results suggest that SFED is an effective treatment modality both in improving symptoms and reducing inflammation associated with EE. This study further shows that SFED has the practical and palatable advantages of allowing table foods in the diet and therefore better acceptability by patients and their families.

We had 3 compelling reasons to study the effect of this novel SFED dietary treatment in children with EE. First, previous studies have shown that eliminating foods based on the results of the radioimmunosorbent test and the skin prick test is not effective in resolving symptoms and esophagitis.[2,3] So instead of using proven allergy to identify food allergens, and in an effort to provide a semblance of a regular diet, we planned to temporarily eliminate 6 foods that are the most common food allergens in children.[20] This diet would circumvent the discomfort and distress of feeding tubes and the monotony of the same liquid diet. Second, this dietary approach to treating EE was assessed to be nutritionally safe and one that was expected to induce short-term remission similar to that when gluten is excluded in celiac disease. Third, although strict, exclusive ELED has been shown to be highly effective in inducing remission in children with EE,[12] compliance remains a problem even when tube feedings are used, as shown in 2 of our excluded patients. The strict ELED places significant financial and social burdens on families because it can cost between $900 and $1500 per month to provide adequate calories for growth in a 20-kg child. The placement and maintenance of the tubes also incurs additional health care costs,[22,23] and leads to an impaired quality of life and also affects social life because most childhood activities revolve around food.[24] By contrast, SFED allows most regular table foods and is therefore better accepted. We found that compliance with SFED was high and potential food cross-contamination was extremely low, and it was less frustrating and disruptive to family life. Finally, once SFED

Table 2. Number of Patients With Initial Symptoms and Response to SFED and ELED

	SFED (N = 35)			ELED (N = 25)		
Symptom	Resolved	Improved	No change	Resolved	Improved	No change
Vomiting	15	5	1[a]	15	3	
Abdominal pain	8	1	1[a]	4	1	
Dysphagia	8			2		
Food impaction	7			1		
Failure to thrive	5			14	1	
Food aversion	2	1	1[a]	Tube fed		
Nausea	4			0		
Diarrhea	2			2		
Cough	2			1		
Halitosis	1					

[a]Same patient who also had no histologic improvement.

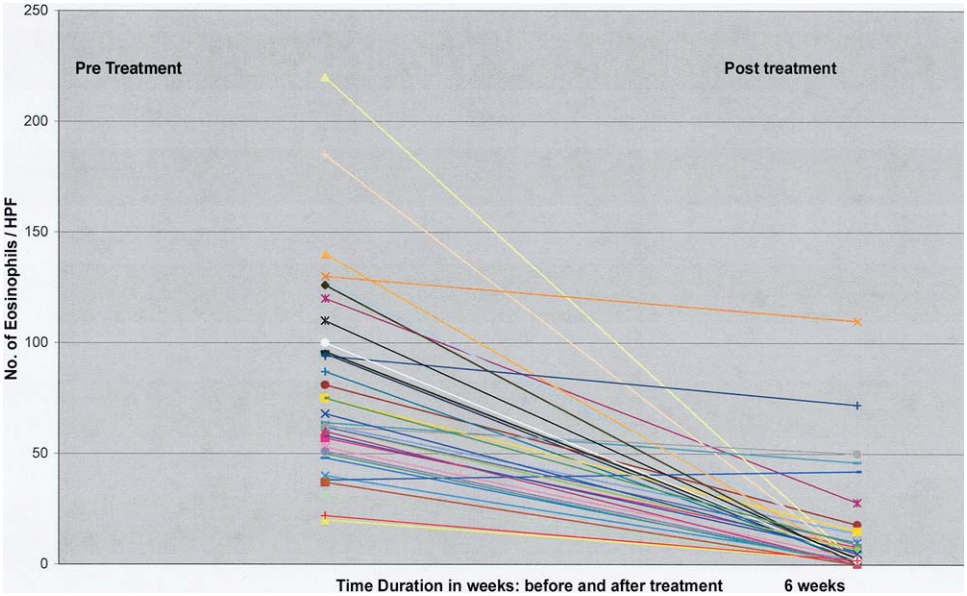

Figure 1. Pretreatment and post-treatment peak eosinophil counts after SFED (N = 35).

achieved remission the subsequent sequential food challenges involved only 6 foods as compared with more than a hundred foods with the ELED.

Those who failed SFED treatment (esophageal eosinophil count >20/HPF) were offered the option of treatment with ELED. Four of these 5 patients showed histologic improvement with elimination of all the intact proteins, thus showing that food proteins other than the 6 excluded ones were involved in causing the esophageal inflammation in the nonresponders. One patient failed the elemental diet and both topical and systemic steroids, indicating a nonallergic cause.

At present there is no standard recommended therapy for EE.[13] The dietary approach is challenging and unpalatable and pharmacologic options have side effects. The ideal treatment is one that leads to long-term clinical and histologic remission, thus preventing potential complications such as esophageal strictures. Our data suggest that temporarily eliminating the most common food allergens such as cow-milk protein, soy, egg, wheat, peanut/tree nuts, and fish is effective at inducing short-term clinical and histologic improvement in a majority of children and may be an effective approach that limits the number of foods for subsequent challenges. Based on our findings, SFED appears to be an effective short-term therapy for children with EE. As an added benefit, this approach reserves other more difficult treatment options including an amino acid elemental formula, allergy test–directed elimination diets, and corticosteroids for the children who fail SFED. However, because this study did not collate long-term follow-up data it is not be possible to predict the eventual outcome in those in whom causal food allergens are identified. For instance, it is not known if tolerance to the incriminating food(s) will develop in time as occurs with cow's-milk protein enterocolitis[25] or whether this is a permanent sensitivity requiring life-long exclusion such as gluten-containing foods in celiac disease.[26]

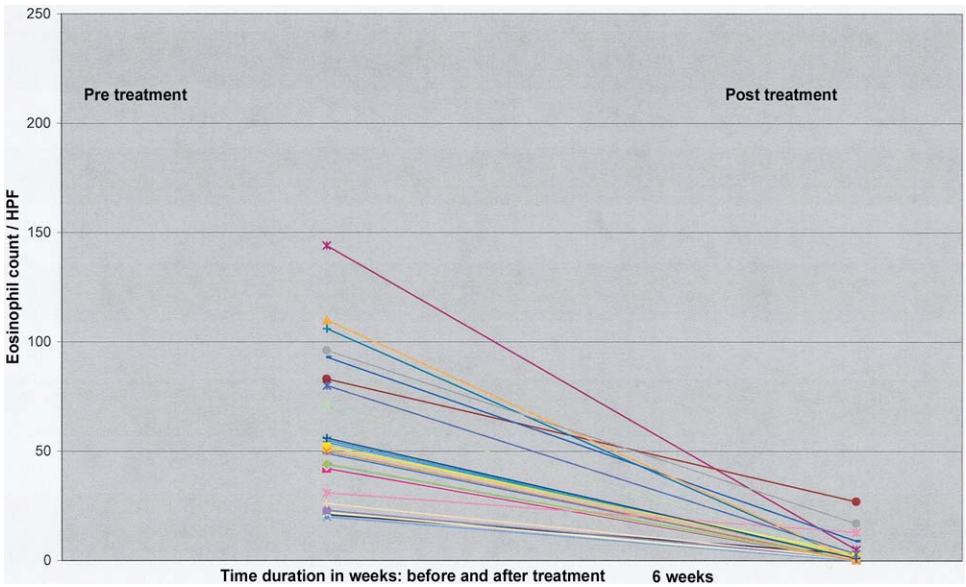

Figure 2. Pretreatment and post-treatment esophageal eosinophil count after ELED (N = 25).

Table 3. Comparison of Histologic Response to Treatment With SFED and ELED

Type of diet	N	Significant improvement (≤10 eosinophil/HPF)		Partial improvement (11–20 eosinophil/HPF)		Treatment failure (20 eosinophil/HPF)		Pre–biopsy examination (peak eosinophil count)	Post–biopsy examination (peak eosinophil count)	*P* value
		N (%)	Peak eosinophil[a]	N (%)	Peak eosinophil[a]	N (%)	Peak eosinophil[a]			
SFED	35	26 (74)	3.1 ± 3.2	3 (9)	15.7 ± 2.1	6 (17)	58.0 ± 29.2	80.2 ± 44.0	13.6 ± 23.8	<.0001
ELED	25	22 (88)	1.6 ± 2.1	2 (8)	15.0 ± 2.8	1 (4)	N/A	58.8 ± 31.9	3.6 ± 6.5	<.001

N/A, not applicable.
[a]Peak eosinophil count: mean for the group ± SD of each group.

The major limitation of this study is the lack of long-term data about identification and exclusion of specific incriminating food allergens and the eventual outcome in patients with EE. The other major shortcoming is in the design of this study. There were several years separating the 2 observational intervention study groups, making meaningful comparison of the efficacy and superiority of one treatment modality over the other almost impossible.

Although this therapy is effective it also presents challenges in appropriately implementing an elimination diet, which is difficult without the active participation of a registered dietitian. To strictly comply with SFED initially and to provide subsequent ongoing active dietary counseling the participation of a registered dietitian is absolutely essential; this, in addition to reducing the risk of food contamination, also ensures a balanced and calorically adequate diet in the absence of several major food proteins in the diet. Effective in 2006, the food allergen and consumer protection legislation requires food manufacturers to clearly identify the presence of 8 food antigens including cow-milk protein, soy, egg, wheat, peanuts, tree nuts, seafood, and shell fish foods on labels. Although this will significantly simplify the process of avoiding food contamination, it will not, unfortunately, eliminate the need for the dietitian.

In summary, our results show that a standard SFED achieves significant histologic improvement in three quarters of children with EE. It offers several substantial advantages by allowing ingestion of solid foods rather than liquid formula alone, it circumvents the discomfort and distress of tube feedings, and it limits the number of potential food allergens that need to be re-introduced subsequent to successful improvement. We believe this treatment approach offers the prospect of a short-term remission, a shorter time to identify the offending food allergen(s), and the potential prospect for long-term cure. Prospective long-term, double-blind, randomized studies are needed to compare the efficacy of different dietary treatments and to address the long-term outcome in patients with EE.

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