

Prospective, comparative effectiveness trial of cow's milk elimination and swallowed fluticasone for pediatric eosinophilic esophagitis

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SUMMARY. Eosinophilic esophagitis (EoE) is a chronic, immune-mediated disease in which food antigens play a key role. Current therapeutic options are limited to long-term steroid medication and dietary elimination of multiple foods, each of which is challenging. Our objective was to compare single food elimination of cow's milk to swallowed fluticasone in pediatric EoE patients. This is a prospective, comparative effectiveness trial of newly diagnosed EoE patients (ages 2–18 years) treated with swallowed fluticasone ($n = 24$) or elimination of cow's milk ($n = 20$). The dual outcome measures of repeat esophageal biopsy (6–8 weeks) and change in Pediatric Quality of Life Inventor (PedsQL) EoE Module and Symptoms Scales were used to assess response to treatment. After 6–8 weeks of treatment, peak esophageal eosinophil counts decreased to below the threshold of 15 eosinophils/high-power field in 64% of patients treated with cow's milk elimination and 80% of patients treated with swallowed fluticasone ($P = 0.4$). Mean PedsQL EoE Module total scores (69 vs. 82; $P < 0.005$) and Total Symptoms scores (58 vs. 75; $P = 0.001$) showed significant improvement with cow's milk elimination. Among children treated with swallowed fluticasone, mean PedsQL EoE Module total scores (64 vs. 75; $P < 0.05$) and Total Symptoms scores (58 vs. 69; $P < 0.01$) were also significantly improved after 6–8 weeks of therapy. Removal of cow's milk from the diet is an effective single food elimination treatment for pediatric patients with EoE as assessed by statistically significant histologic and symptomatic improvement. Cow's milk elimination may be more desirable for EoE patients who do not want to take chronic, long-term steroid medications.

KEY WORDS: child, comparative effectiveness, eosinophilic esophagitis, patient-reported outcomes, PedsQL, therapeutics.

ABBREVIATIONS: EoE, eosinophilic esophagitis; EREFS, Endoscopic Reference Score; FDA, Food and Drug Administration; hpf, high-power field; HRQOL, health-related quality of life; NHANES, National Health and Nutrition Examination Survey; PedsQL, Pediatric Quality of Life Inventor; PPI, proton pump inhibitor; PRO, patient-reported outcome

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic condition that is a result of immune-mediated inflammation of

the esophagus. It is generally accepted today that EoE is directly related to food antigens.¹ Diagnosis of pediatric EoE is increasing at an alarming rate such that recent epidemiologic data indicate that EoE is now a leading cause of dysphagia.^{2,3} Other investigators have reported that the prevalence of EoE is now approaching that of Crohn's disease.^{4–6} Complications of EoE include esophageal fibrosis, strictures, esophageal dysmotility, and lower health-related quality of life (HRQOL).^{7–9}

Treatment of EoE consists of dietary changes, corticosteroids, and if necessary esophageal dilation.

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There is evidence to support restrictive diets including targeted elimination of foods that are 'positive' by skin prick allergy testing or atopy patch testing; an empiric 'six-food' elimination diet in which all foods containing egg, milk, wheat, soy, peanut, tree nuts, and seafood are removed; and an elemental formula diet.^{10–12} Treatment with medication entails daily administration of topical corticosteroid preparations. Typically, patients take fluticasone or budesonide, but rather than inhaling the medications, they are instructed to swallow the doses.^{13,14} These therapies are effective in 50–90% of patients; however, as a chronic condition, EoE requires ongoing intervention and therapy. Patients typically relapse in symptoms or histological findings after the diet or medications are discontinued.^{15,16}

Some experts have recommended dietary therapy as first-line therapy for EoE in pediatric patients for several reasons.^{17,18} First, studies focusing on dietary intervention have found that pediatric patients tend to do well once the food allergens are identified.¹⁶ Also, there is concern about the side effects of chronic use of corticosteroids especially in children. There are also potential challenges associated with dietary therapy. Current recommended diets are challenging. Furthermore, traditional allergy tests (skin prick testing and atopy patch testing) frequently cannot identify inciting food allergens, and as a result, many dietary therapies are empiric and require multiple repeat endoscopies.¹⁷

An effective, less restrictive dietary change to treat EoE would be useful. Sequential re-introduction of foods after the six-food elimination diet and identification of causative foods by skin prick test suggest that milk is the most common problem food.¹⁷ Serological assays show that cow's milk sensitization is common, but the results have not been correlated with response to diet.¹⁸ In a retrospective study of pediatric patients, those who removed only cow's milk from the diet achieved histologic remission.¹⁹ Our objective was to prospectively observe pediatric patients newly diagnosed with EoE, who removed only cow's milk from the diet, and compare their clinical and histologic outcomes to patients who were treated with a standard medication regimen.

PATIENT AND METHODS

Patients

Patients were recruited from the Pediatric Gastroenterology clinic at Nationwide Children's Hospital between November, 2012 and March, 2014 for a prospective, comparative effectiveness study using a quasi-experimental nonequivalent groups design.²⁰ Inclusion criteria included new diagnosis of EoE, esophageal biopsy with at least 15 eosinophils/high-power field (hpf), and normal stomach and duodenal

biopsies. Patients were treated with either swallowed fluticasone or dietary elimination of cow's milk. Both groups were treated with proton pump inhibitor (PPI).¹⁴ Treatment group was determined by the preference of the physicians and patients. Families were informed of the expected response rates to available treatments for EoE. Physicians also explained the pros and cons of both treatment options to the patients and families. The study was approved by the Institutional Review Board at Nationwide Children's Hospital, and informed consent was obtained from all patients.

Study procedures

Our study design is detailed in Figure 1. At enrollment (Visit 1), patients and families completed the Pediatric Quality of Life Inventor (PedsQL) EoE Module and the EoE Symptoms Scales it encompasses.²¹ Cow's milk intake was assessed for all participants by using a National Health and Nutrition Examination Survey (NHANES)-based questionnaire. Parents of patients who were treated with a cow's milk elimination diet also met with a nutritionist at this visit. Visit 2 occurred at 6–8 weeks when repeat upper gastrointestinal endoscopy with esophageal biopsy was performed in addition to administration of the PedsQL EoE Module and a self-reported adherence questionnaire.

Statistical analyses

There were two primary study outcomes: (i) change in esophageal eosinophil count and (ii) change in PedsQL EoE Total Symptoms score from the PedsQL EoE Module. Patients were designated as histologic responders (<15 eosinophils/hpf) versus nonresponders (≥15 eosinophils/hpf) on repeat biopsy (6–8 weeks) and compared using the chi-square test. The mean change in esophageal eosinophils was compared using *t*-test with Levine's test for verification of equality of variance assumption. We used exact logistic regression to evaluate the roles of adherence and treatment, and any interaction between the two factors, in histologic response.

The second outcome was change in EoE-specific HRQOL as measured by the PedsQL EoE Module.²¹ The 33-item PedsQL EoE Module encompasses seven scales: (1) Symptoms I (six items; chest/throat/stomach pain, gastroesophageal reflux and nausea/vomiting); (2) Symptoms II (four items; trouble swallowing); (3) Treatment (five items; treatment barriers); (4) Worry (six items; worries about treatment and disease); (5) Communication (five items; communication with others about EoE); (6) Food and Eating (four items; food and eating allergies and limitations); and (7) Food Feelings (three items; emotions associated with food allergies). A 5-point Likert scale (0 =

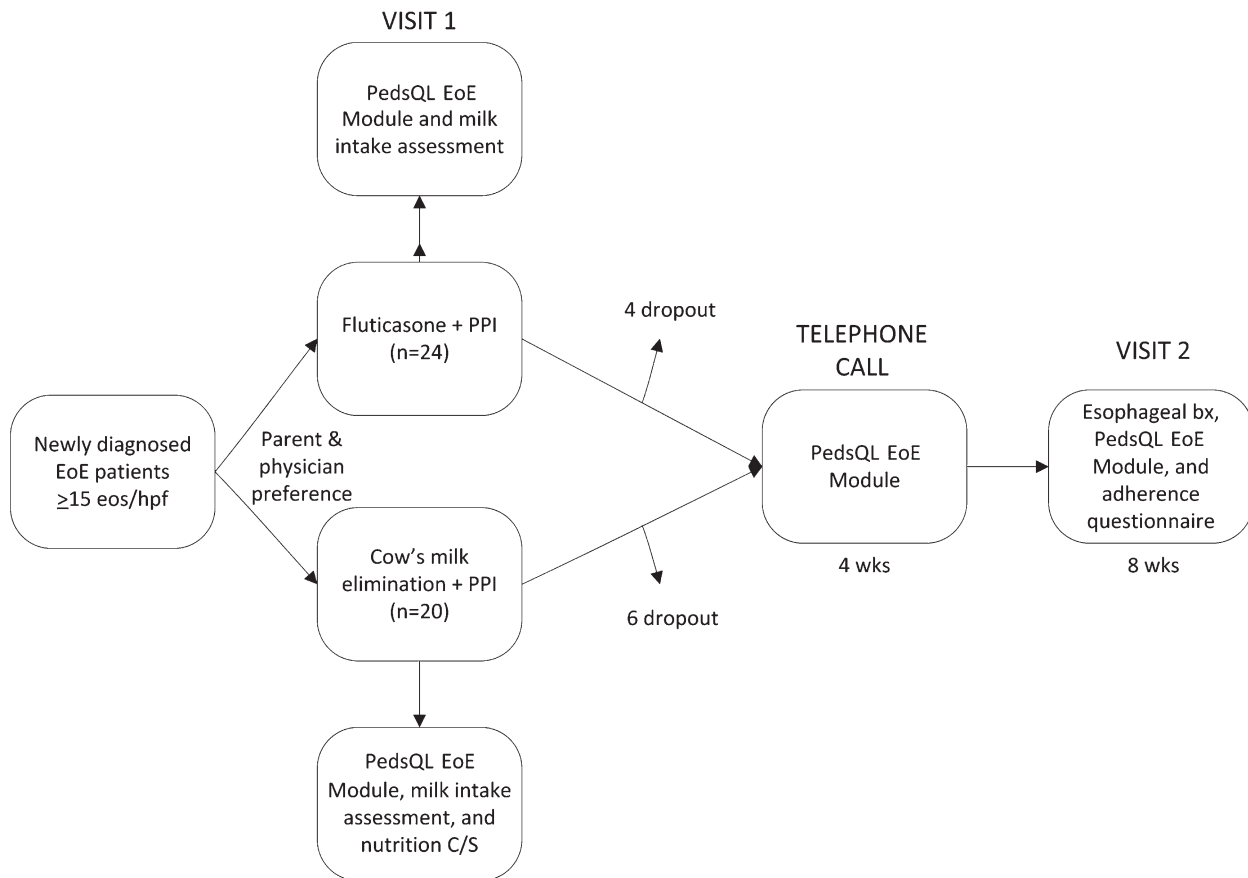


Fig. 1 Flow diagram of study visits.

never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem) was used for reporting. Items are linearly transformed to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0). Using this measure, higher scores indicate fewer problems or symptoms. The scaled PedsQL EoE Total Symptoms score is based on the sum of the responses to each item within the Symptoms I and Symptoms II Scales divided by the number of items for which a response was provided.

Mean change in PedsQL EoE Total Symptoms Scores was compared between treatment groups using a *t*-test with Levine's test for verification of equality of variance assumption. The scores for individual patients before and after treatment were compared by using paired *t*-test. Effect sizes were calculated using Cohen's *d* formula. PedsQL EoE Module scores were used as a secondary outcome. The scaled PedsQL EoE Module total score comprised the sum of each response (33 and 27 items for those with and without food allergy, respectively). In order to calculate each scale score, the sum of transformed results was divided by the number of items within the domain for which a response was provided. The paired *t*-test was also used to compare each scale score before and after treatment. Chi-

square tests were utilized to test for differences in proportions when expressed as percentages. Effect size was measured using Cramer's phi.

Additional analyses were performed in order to compare the clinical characteristics of responders and nonresponders to each treatment regimen. The chi-square test was used to compare categorical variables, and Kruskal–Wallis test and analysis of variance (ANOVA) were used to compare nonparametric and parametric continuous variables. Based on the results of these analyses, the group of patients who presented with food impaction was also analyzed separately. For these analyses, the chi-square test was used to compare categorical variables, and Mann–Whitney *U*-test and *t*-tests were used to compare nonparametric and parametric continuous variables, respectively. Statistical testing was performed using IBM SPSS Statistics 21 (IBM Corporation, Armonk, NY, USA).

RESULTS

After receiving information describing the two treatment options, more families expressed interest in treatment with swallowed fluticasone ($n = 24$)

compared with 20 patients recruited for the cow's milk elimination diet. Four patients in the fluticasone group (17%) and six patients (30%) in the cow's milk elimination group withdrew from the study before completing repeat esophageal biopsy ($P = 0.5$). Reasons for study withdrawal included unavailability of cow's milk substitution foods, unwillingness for repeat endoscopy, inability to contact the family, or failure to perform repeat endoscopy within the study period. When patients were compared at the time of enrollment, mean ($\pm$ SD) PedsQL EoE Total Symptoms scores were 58 ($\pm$ 19) for the subjects treated with fluticasone and 58 ($\pm$ 17) for the subjects eliminating cow's milk ($P = 0.9$) (Table 1). Scores for the Symptoms II Scale were significantly lower (worse) for patients who enrolled in cow's milk elimination group ($P < 0.001$). At enrollment, the peak esophageal eosinophil count was slightly higher but not statistically different for those taking fluticasone ($63 \pm 33/\text{hpf}$) compared with those eliminating cow's milk ($46 \pm 24/\text{hpf}$) ($P = 0.06$) (Table 1). In contrast, the observation of white plaques in the esophagus was more common in the group treated with cow's milk elimination ($P < 0.001$) (Table 1).

After treatment, mean esophageal eosinophil counts decreased significantly in both study groups (Table 2A and B). Nine subjects treated with diet (64%) and 16 participants treated with fluticasone (80%) had decreases in esophageal eosinophil counts to below the threshold of 15 eosinophils/hpf on repeat biopsy ($P = 0.4$). The mean ($\pm$ SD) decrease in esophageal eosinophil counts in patients treated with swallowed fluticasone was 55 ($\pm$ 37)/hpf compared with 29 ($\pm$ 33)/hpf in those treated with dietary elimination of cow's milk ($P = 0.04$) (Fig. 2). These data were also analyzed as percent change in esophageal eosinophil count, and the results were the same. Strict adherence to diet was reported by 79% of those treated with milk elimination. Seventy percent of

patients taking fluticasone reported that they missed less than one dose of the medication each week. The response rates in adherent patients were 81% for cow's milk elimination and 79% for fluticasone. When dietary treatment was adjusted by adherence, it decreased the odds of a histologic response, but the results were not significant (odds ratio 0.39, $P = 0.4$). There was not a significant interaction between treatment group and adherence.

Symptom scores improved (higher scores) significantly during both treatments. For patients treated with cow's milk elimination, PedsQL EoE Total Symptoms scores improved from mean ($\pm$ SD) of 58 ($\pm$ 21) to 75 ($\pm$ 15) after treatment ($P < 0.001$) (Table 2A). The patients who eliminated cow's milk from the diet also showed significant improvement in both PedsQL Symptoms I and Symptoms II Scale scores ($P = 0.001$ and $P = 0.03$, respectively) (Table 2A). Mean PedsQL EoE Total Symptoms scores improved by 17 ($\pm$ 12) in subjects treated with cow's milk elimination as compared with 11 ($\pm$ 17) in subjects treated with fluticasone ($P = 0.3$) (Fig. 3). Improvement in PedsQL EoE Module Symptoms I Scale scores showed a medium correlation with decrease in esophageal eosinophil counts ($R = 0.35$, $P = 0.05$) (Fig. 4). Patients who were treated with cow's milk elimination also had improvement in PedsQL EoE Module total scores ($P = 0.003$), suggesting improvement in quality of life measures as well (Table 2A).

We compared baseline characteristics, clinical features, and PedsQL EoE Module scores in patients responding to treatment with swallowed fluticasone or cow's milk elimination with those who did not respond to their treatment in order to identify any predictive clinical features. The only clinical feature that was associated with response to either treatment regimen was food impaction (Table S1). Patients who presented with food impaction were less likely to have

Table 1 Characteristics of study participants at enrollment

	Fluticasone ($n = 24$)	Diet ($n = 20$)	P -value†
Median age, years (range)	12 (2–17)	13 (2–17)	0.7
Male gender, n	15 (63%)	13 (65%)	0.9
Presented with food impaction, n	6 (25%)	9 (45%)	0.2
Reported food allergy, n	13 (56%)	7 (35%)	0.2
Milk intake score‡, mean ($\pm$ SD)	10 ($\pm$ 3.4)	11 ($\pm$ 3.4)	0.5
Mucosal appearance, n			
Normal	8 (33%)	3 (15%)	0.2
Furrowing	15 (63%)	17 (85%)	0.1
White plaques	6 (25%)	16 (80%)	<0.001
Peak esophageal eosinophils/hpf, mean ($\pm$ SD)	63 ($\pm$ 33)	46 ($\pm$ 24)	0.06
PedsQL Total Symptoms score, mean ($\pm$ SD)	58 ($\pm$ 19)	58 ($\pm$ 17)	0.9
Symptoms I	57 ($\pm$ 21)	65 ($\pm$ 22)	0.3
Symptoms II	83 ($\pm$ 16)	54 ($\pm$ 27)	<0.001
PedsQL EoE Module score, mean ($\pm$ SD)	65 ($\pm$ 16)	67 ($\pm$ 14)	0.7

† P -values obtained by using Mann–Whitney U -test to compare medians, chi-square test for categorical variables, and Student's t -test to compare means. ‡Score based on responses to National Health and Nutrition Examination Survey (NHANES) assessment of milk intake. EoE, eosinophilic esophagitis; hpf, high-power field; PedsQL, Pediatric Quality of Life Inventor; SD, standard deviation.

Table 2 Clinical measurements at baseline and after treatment for patients in the (A) cow's milk elimination group and (B) fluticasone group

(A)	Baseline (<i>n</i> = 14)	After treatment (<i>n</i> = 14)	<i>P</i> -value†	Effect size‡
Peak esophageal eosinophils/hpf, mean (± SD)	46 (± 25)	17 (± 16)	0.006	1.4
PedsQL Total Symptoms score	58 (± 21)	75 (± 15)	0.001	0.93
Symptoms I	70 (± 22)	86 (± 15)	0.001	0.85
Symptoms II	48 (± 25)	63 (± 24)	0.03	0.61
PedsQL EoE Module score	69 (± 14)	82 (± 12)	0.003	1.0
Treatment	81 (± 17)	88 (± 17)	0.1	0.41
Worry	74 (± 18)	86 (± 17)	0.07	0.68
Communication	82 (± 23)	93 (± 13)	0.06	0.59
Mucosal appearance, <i>n</i> (%)§				
Normal	1 (7%)	7 (50%)	0.03	0.47
Furrowing	13 (93%)	5 (36%)	0.004	0.60
White plaques	3 (21%)	4 (29%)	1	0.08

(B)	Baseline (<i>n</i> = 20)	After treatment (<i>n</i> = 20)	<i>P</i> -value†	Effect size‡
Peak esophageal eosinophils/hpf, mean (± SD)	68 (± 33)	13 (± 23)	<0.006	1.9
PedsQL Total Symptoms score	58 (± 20)	69 (± 19)	0.008	0.56
Symptoms I	57 (± 22)	83 (± 16)	0.001	1.4
Symptoms II	56 (± 29)	64 (± 27)	0.2	0.29
PedsQL EoE Module score	64 (± 17)	75 (± 20)	0.04	0.59
Treatment	70 (± 28)	74 (± 30)	0.6	0.14
Worry	69 (± 25)	73 (± 30)	0.5	0.15
Communication	67 (± 29)	79 (± 24)	0.1	0.45
Mucosal appearance, <i>n</i> (%)§				
Normal	7 (35%)	9 (45%)	0.5	0.10
Furrowing	12 (60%)	6 (30%)	0.06	0.30
White plaques	5 (25%)	1 (5%)	0.08	0.28

†*P*-values were obtained by using chi-square test for categorical variables and paired *t*-test to compare means. ‡Effect size was calculated using Cohen's *d* to compare mean eosinophil counts and scores before and after treatment. Effect sizes are considered small (0.2), medium (0.5), and large (0.8). §Effect size was measured using Cramer's phi and interpreted as small (0.1), medium (0.3), and large (0.5) in magnitude. EoE, eosinophilic esophagitis; hpf, high-power field; PedsQL, Pediatric Quality of Life Inventor; SD, standard deviation.

<15 eosinophils/hpf on esophageal biopsy after treatment compared with those who did not have food impaction (47% and 95% response, respectively, *P* = 0.002) (Table 3). Further examination of the participants who had food impaction showed that they had slightly lower scores (indicating more frequent problems) for the Symptoms II Scale, which measures 'trouble swallowing' (*P* = 0.05) (Table 3).

Although symptom scores and HRQOL improved in patients treated with elimination of cow's milk and the majority of patients achieved histologic remission, only 64% of those who completed the study answered 'yes' when asked if they thought that they could continue this diet on a long-term basis. In contrast, 79% of patients who were taking swallowed fluticasone expressed that they would be willing to continue this treatment.

DISCUSSION

Although exploratory, our study is the first prospective, pediatric EoE comparative effectiveness study to demonstrate that cow's milk elimination is an effective therapy based on not only resolution of esophageal eosinophils but also improvement in EoE symptoms and EoE-specific HRQOL. EoE is an increasingly common chronic disorder that is

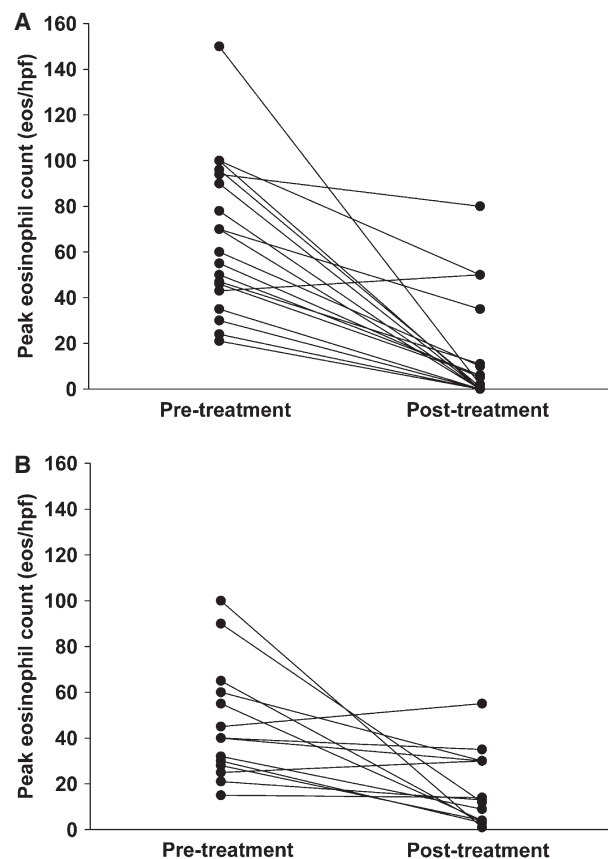


Fig. 2 Peak esophageal eosinophil counts at diagnosis and after treatment with fluticasone (A) and milk elimination diet (B).

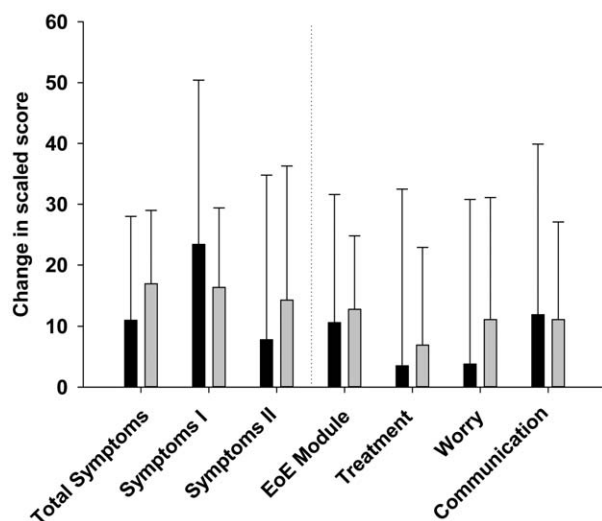


Fig. 3 Mean change in PedsQL^M EoE Module Total Symptoms scores and total scores as well as specific scale scores after treatment with fluticasone (■) and milk elimination diet (▒).

currently treated with long-term restrictive diets and/or daily inhaled corticosteroid preparations taken orally and swallowed. Some families may not have the resources to maintain a complicated allergen-free diet and/or have beliefs about long-term use of (steroid) medications that affect adherence. A simpler dietary treatment regimen would be desirable for these patients. Our study shows that elimination of foods that contain cow's milk is an effective treatment both clinically and histologically for a subgroup of patients.

In addition to being the first study to show prospectively that single food dietary elimination for children with EoE is an effective therapy, we have demonstrated that the PedsQL EoE Module and Symptoms Scales can be successfully utilized as responsive patient-reported outcomes (PROs) in EoE clinical

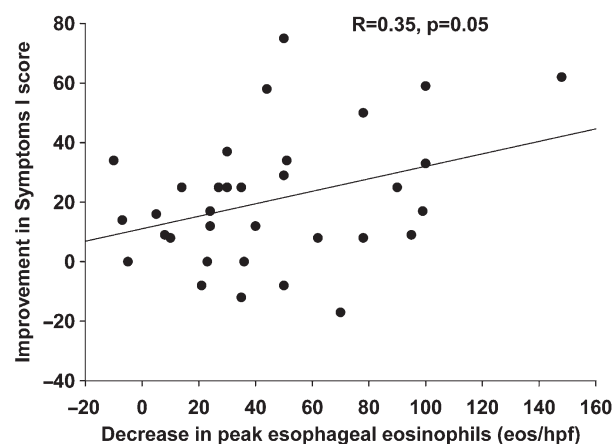


Fig. 4 Relationship between improvement in PedsQL EoE Symptoms I Scale scores and decrease in peak esophageal eosinophils after treatment with fluticasone or elimination of cow's milk from the diet.

Table 3 Baseline characteristics of patients who presented with food impaction compared with the rest of the cohort

	Food impaction (n = 15)	No impaction (n = 19)	P value†
Median age, years (range)	13 (7–17)	7.0 (2–17)	0.02
Male gender, n	13 (87%)	15 (79%)	0.6
Mucosal appearance			
Normal	2 (13%)	6 (32%)	0.3
Furrowing	13 (87%)	12 (63%)	0.2
White plaques	4 (25%)	4 (21%)	1
Peak eosinophils/hpf, mean (± SD)	59 (± 30)	59 (± 34)	1
PedsQL Total Symptoms score	55 (± 22)	60 (± 18)	0.5
Symptoms I	67 (± 23)	58 (± 22)	0.3
Symptoms II	43 (± 30)	61 (± 23)	0.05
PedsQL EoE Module‡	65 (± 15)	67 (± 16)	0.7
Treatment	77 (± 18)	72 (± 29)	0.6
Worry	71 (± 18)	71 (± 26)	1
Communication	75 (± 27)	71 (± 28)	0.7
Treatment responder§, n	7 (47%)	18 (95%)	0.002

†Chi-square test was used to compare categorical variables and Mann-Whitney *U*-test and *t*-test were used to compare nonparametric and parametric continuous variables, respectively. ‡Scores measured before treatment. §Having <15 eosinophils/hpf after treatment. EoE, eosinophilic esophagitis; hpf, high-power field; PedsQL, Pediatric Quality of Life Inventor; SD, standard deviation.

trials. Recent guidelines by the Food and Drug Administration (FDA), some of which are specific for pediatric EoE, as well as legislative changes, support an emerging paradigm shift in pediatric clinical trials toward PROs.^{22,23} The improvement in PedsQL EoE Symptoms scores by a mean of 17 points during the 6- to 8-week study period was statistically significant for patients who were treated with cow's milk elimination diet. However, statistical significance is not the same as a clinically meaningful change. Disease-specific clinically important differences in HRQOL have not been determined for EoE. Franciosi and colleagues were able to distinguish between patients with active disease and remission when they administered the PedsQL EoE Module to a large group of patients (and parents).²¹ They found that in patients with <15 eosinophils/hpf compared with ≥15 eosinophils/hpf, the difference in total scores for pediatric self-report and parent proxy-report was 5.7 ($P < 0.05$ and $P < 0.01$, respectively). These data suggest that clinically meaningful changes in scores for patients with EoE may be detected with small changes in PedsQL scores. Finally, the effect size, a standardized measure of the magnitude of differences, provides further support that the outcomes we are reporting for patients on cow's milk elimination diet are relevant.²⁴ The effect sizes for change in esophageal eosinophils and change in PedsQL EoE Module scores after treatment with cow's milk elimination (0.59–1.4) can be interpreted as medium to large.²⁴

In addition to PRO data, we utilized peak esophageal eosinophils as a primary outcome based on current evidence for treatment standards.¹ However, it is not clear that this is the best measure of disease severity. The patients in our study who were treated with cow's milk elimination had slightly lower peak eosinophil counts at baseline, but some of their clinical features may suggest more severe disease. First, visual examination of the esophagus revealed the finding of white plaques more frequently in the patients who eliminated cow's milk ($P = 0.001$). Hirano created an endoscopy score, the EoE Endoscopic Reference Score (EREFS), based on grading the four major esophageal features (rings, furrows, exudates, and edema).²⁵ He showed that the first three features, which include white plaques/exudates, can be a reliable indicator of clinical differences between patients and may be a marker of disease severity.²⁶ Second, although the difference was not significant, more patients in our study who were treated with elimination of cow's milk had presented with food impaction. In contrast with esophageal eosinophil counts, food impaction was believed to be a clinical indicator of EoE severity and correlated with reduced esophageal distensibility as measured by high-resolution impedance planimetry using the functional lumen-imaging probe.²⁷

The natural history of EoE is not clear, but it is now believed to be a chronic disease in most cases.^{8,15,16} Thus, it is important to consider both the likelihood of achieving response to treatment and the ability or willingness to adhere with therapy for an extended period of time. Franciosi and colleagues explored patient and parent concerns regarding food and treatment regimens in order to develop their disease-specific quality of life instrument.²⁸ The social impact of being different because of diet changes and the difficulties of restricted diets were issues raised in focus interviews.²⁸ Medication use was also reported to be difficult because of problems remembering to take medications.²⁸ In a single study of medication adherence in EoE and eosinophilic gastrointestinal disorders, 30% of patients reported that they did not adhere to medication therapy.²⁹ The asthma literature emphasizes the concerns that patients have about inhaled corticosteroids that may interfere with adherence to daily medication regimens. Specific recurrent concerns about taking inhaled corticosteroids included worries about side effects, worries about getting addicted, and failure to understand the medication regimen.³⁰ The proportions of EoE patients who reported eating a food that is not on the diet were 30% and 37% in the two published studies.^{29,31} Most patients with EoE are not aware of a direct effect on specific food ingestion. This may add to the difficulties with adherence to even the least restrictive diet. It is likely that patients receiving long-term dietary treatment for EoE will need multifaceted,

ongoing support from the members of the clinical care team (dietitians, primary care physicians, and specialists).

For many diseases, different phenotypes can be observed based on patterns of clinical features and response to treatment. The possibility of phenotypes for EoE patients has been proposed, but the nature of these differences has not yet been described.³² Our study, although limited in size, suggests that patients with food impaction could be a phenotype that is less responsive, or takes more time to respond, to treatment. As a group, these patients were older and had lower scores (more symptoms) on the PedsQL Symptoms II Scale (trouble swallowing) than patients who did not have food impaction.

We recognize three possible limitations of this study and will present our view of each in this section. First, a subgroup of patients with esophageal eosinophilia responsive to PPI has been described, and treatment with PPI alone for 8–12 weeks is recommended to identify these patients.¹ Recent studies have shown that clinical features are the same in both disease processes, suggesting that PPI responsive EoE is a subgroup of EoE.³³ In our study, all patients were treated with PPI in combination with swallowed fluticasone or dietary elimination of cow's milk. Thus, response to PPI is not separated from response to swallowed fluticasone or cow's milk elimination, so our high response rate to both treatments may include PPI benefits.³⁴ A second limitation of our study was that treatment was not randomized. We made this choice intentionally because treatment with a restricted diet is something that patients have strong preferences about such that it is difficult to place patients into a random group and recommend this therapy. While the nonrandomized design can introduce selection bias in some studies, we believe that important inferences can still be made. Analyses at baseline suggested that our study groups were not significantly different. Nonrandom allocation could also affect adherence and HRQOL responses, but in our study, this would be true for patients treated with swallowed steroid also. Finally, the small sample size in our study could be another limitation. In order to generalize the results, we used effect size to interpret the findings. The large effect sizes that we found suggest meaningful changes with milk elimination treatment.

In conclusion in this exploratory study, single food elimination of cow's milk has demonstrated not only histologic response (<15 eosinophils/hpf) in a significant proportion of our patients (64%) but also improvement in the PedsQL EoE Module and Symptoms Scales scores. Our results suggest that cow's milk elimination is an effective treatment option that should be considered as a first-line therapy for pediatric patients with EoE. Larger prospective studies are needed to validate our findings.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Characteristics of responders and non-responders treated with either regimen.