

Elemental Diet Is an Effective Treatment for Eosinophilic Esophagitis in Children and Adolescents

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OBJECTIVE: Eosinophilic esophagitis (EoE), a disorder characterized by eosinophilic infiltration of the esophageal mucosa, has been defined in large part through published case reports and series leading to ambiguity in both diagnostic and treatment options. Corticosteroids, cromolyn, and elemental diet have all been reported as successful treatments for EoE. In this study, we sought to accurately define a population of patients with EoE and then assess their response to elemental diet.

METHODS: A series of patients with chronic symptoms of gastroesophageal reflux disease and an isolated esophageal eosinophilia on esophagogastroduodenoscopy (EGD) were identified. Therapy with a proton pump inhibitor was instituted for 3 months, followed by repeat EGD when symptoms persisted. A 24-h pH probe study was performed, and those with significantly abnormal studies were excluded. The remaining patients were diagnosed with EoE and placed on an elemental diet for 1 month, followed by a repeat EGD.

RESULTS: Of 346 patients with chronic gastroesophageal reflux disease symptoms and eosinophils on esophageal biopsy, 51 (14.7%) were ultimately diagnosed with EoE. There was significant improvement in vomiting, abdominal pain, and dysphagia after the elemental diet. The median number of esophageal eosinophils per high-powered field (HPF) decreased from 33.7 before the diet to 1.0 after the diet ($p < 0.01$). The average time to clinical improvement was 8.5 days.

CONCLUSIONS: Elemental diet resulted in striking improvement in both symptoms and histologic evidence of disease in children and adolescents with EoE, as identified by strict diagnostic criteria. (Am J Gastroenterol 2003;98:777-782. © 2003 by Am. Coll. of Gastroenterology)

INTRODUCTION

Eosinophilic esophagitis (EoE) is a disease characterized by an isolated, severe esophageal eosinophilia that occurs in adults and in children. The symptoms of children with EoE are often difficult to distinguish from those who have gas-

troesophageal reflux disease (GERD) and include vomiting, regurgitation, nausea, epigastric pain, heartburn, and dysphagia. In both groups, the symptoms typically improve with acid blockade; however, whereas patients with GERD generally become symptom free and demonstrate a resolution in their esophagitis, children with EoE almost always continue to exhibit clinical symptoms and display no histologic improvement despite aggressive acid blockade.

The spectrum of EoE has been described predominantly by case reports and case series. However, in the majority of these reports, there has been considerable variability in the criteria used to define EoE. Although effective treatment regimens for EoE have also been reported, these series are also limited by a lack of consistent outcome measures.

The aims of this study were to accurately define a population of patients with EoE, to study the effect of aggressive acid blockade on EoE, and to evaluate the treatment of EoE patients with dietary restriction using a complete elemental diet.

MATERIALS AND METHODS

This study was conducted from January 1, 1997, to January 1, 2000, in the Division of Gastroenterology and Nutrition at the Children's Hospital of Philadelphia. Patients were initially identified if they had chronic GERD symptoms (3 months or more), normal upper GI anatomy based on barium upper GI series, and evidence of an isolated esophageal eosinophilia by esophagogastroduodenoscopy (EGD) with biopsy. GERD symptoms included vomiting/regurgitation, epigastric pain, or at least two of the following: heartburn, water brash, globus, chest pain, dysphagia, nighttime cough, feeding disorder, or irritability. Symptoms were assessed by questionnaire and patient interview, completed by the parents and the patients together, and recorded by the physician. Patients with prior abdominal surgery or disorders of other organ systems (neurologic, cardiac, renal, or endocrine) were excluded.

EGD included visual inspection of the esophagus, stomach, and duodenum, as well as at least three biopsies from

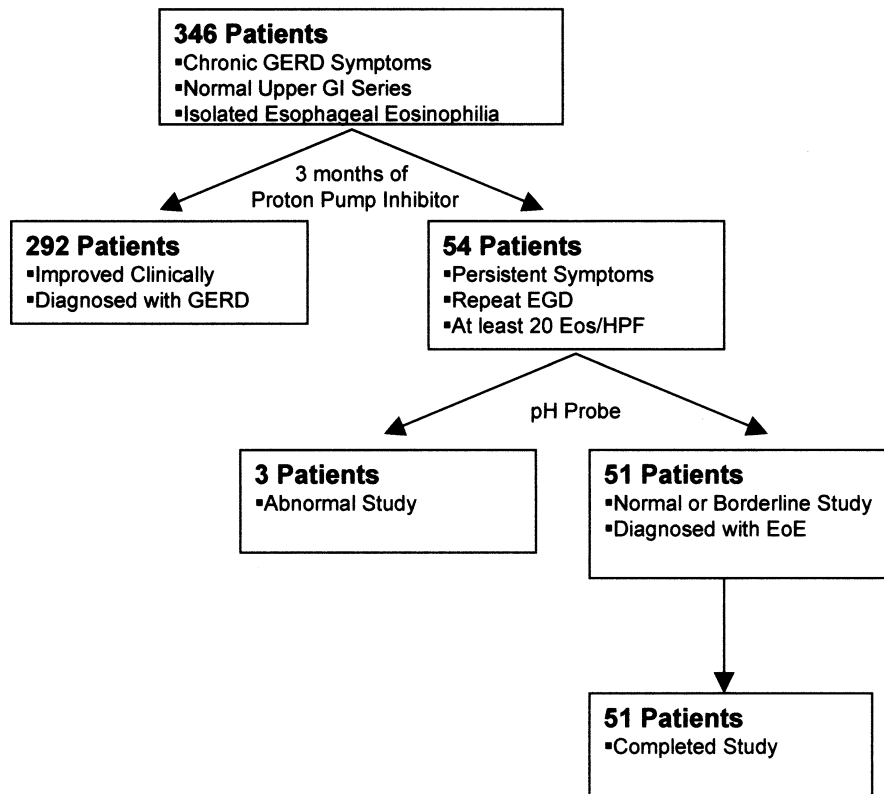


Figure 1. Diagnostic algorithm for EoE.

the distal esophagus (3–5 cm from the lower esophageal sphincter), the gastric antrum, and the duodenum. All biopsies were reviewed by board-certified pathologists who reported the number of eosinophils visible in the most severely affected microscopic high-powered field (HPF) equivalent to $\times 40$ magnification. Up to 10 eosinophils/HPF in the gastric antrum were considered normal if in the basal region of the lamina propria, and up to 25 eosinophils/HPF were considered normal in the duodenum, based on previously published data (1). Other histologic features noted included the presence of neutrophils, basal cell hyperplasia, papillary length, and abscess formation.

Once identified, the patients were placed on a proton pump inhibitor at a dose of at least 1 mg/kg/day (maximum 20 mg *b.i.d.*). Those with symptoms that persisted after 3 months of therapy underwent follow-up EGD. Patients with 20 or more esophageal eosinophils per HPF in conjunction with normal antral and duodenal biopsies underwent a 24-h pH probe esophagram. Patients with pH studies demonstrating no more than infrequent, brief episodes of GERD were diagnosed with EoE and entered into the study. The remaining patients were diagnosed with GERD (Fig. 1).

Once entered, patients were given a diet consisting of an elemental formula, Neocate 1+ (SHS North America, Gaithersburg, MD), which consisted of free amino acids, corn syrup solids, and medium-chain triglyceride oil. Patients were also allowed to take water and one fruit (either grape or apple) and its corresponding pure juice. A nutri-

tionist determined the formula volume necessary to provide adequate calories. The formula was delivered orally or via nasogastric tube based on the patients' ability and willingness to drink the formula. Patients continued to receive proton pump inhibitors. The patients were followed for clinical improvement. While receiving the elemental formula, patients were contacted weekly for review of symptoms and assessment of weight. If a patient demonstrated weight loss, the volume of feedings was increased until weight was shown to have stabilized. As a result, no patients lost weight by the completion of the study. A repeat EGD was performed 1 month after instituting the study diet.

Data were analyzed using the Wilcoxon sign-rank test for continuous variables and the χ^2 test for dichotomous variables. Statistical comparisons were made using the statistical software package Stata 7.0 (Stata, College Station, TX).

RESULTS

During the study period, 346 patients were identified with GERD symptoms and at least one esophageal eosinophil on EGD. Of these, 281 (81.2%) demonstrated clinical improvement on proton pump inhibitor therapy. All of these patients had less than 20 esophageal eosinophils per HPF by biopsy. Eleven patients refused participation in the study. The remaining 54 patients (15.6%) continued to have significant symptoms despite proton pump inhibitors. All of these patients had 20 or more esophageal eosinophils per HPF with

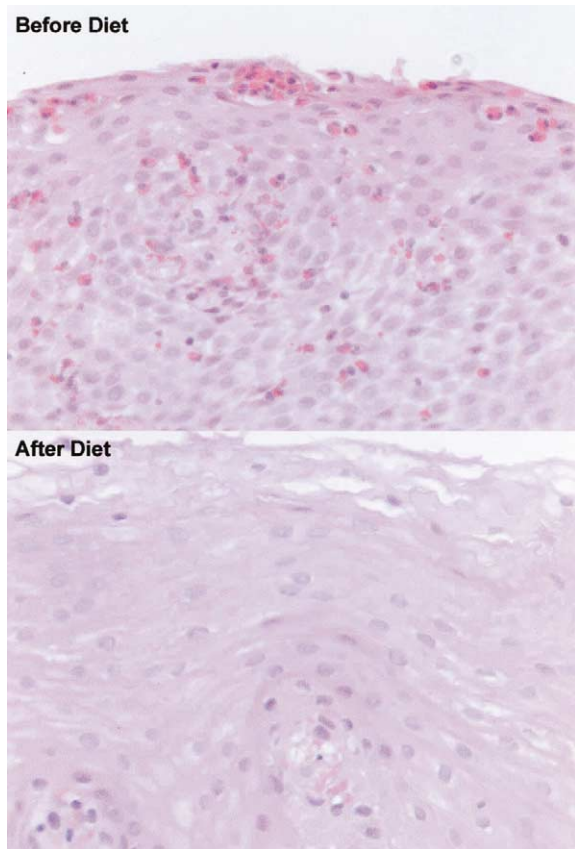


Figure 2. Esophageal biopsies of a patient with EoE before and after treatment with elemental diet (hematoxylin and eosin, original magnification, $\times 40$).

normal antral and duodenal biopsies. Three of the 54 patients had abnormal pH probe esophagrams (more than 6% of the study time with an esophageal pH < 4) and were excluded. The remaining 51 patients were diagnosed with EoE and began therapy with the elemental diet. No patients who began the elemental diet dropped out of the study. The demographic characteristics of the 51 patients are summarized in Table 1.

Table 1. Characteristics of Patients With Eosinophilic Esophagitis

Male/female	33/18
Age (yr) (range)	8.3 \pm 3.1 (3–16)
Race (white/black/Hispanic/Asian/other)	36/8/4/2/1
First-degree relative with atopic disease (%)	20 (39)
Symptoms (%)	
Epigastric pain	40 (78)
Vomiting/regurgitation	36 (71)
Heartburn	27 (53)
Atopic disease (asthma/eczema/allergic rhinitis)	26 (51)
Water brash	11 (22)
Globus	9 (18)
Dysphagia	7 (14)
Night cough	5 (10)
Chest pain	4 (8)
Irritability	3 (6)

Table 2. Number of Patients With Symptoms Before (Prediet) and After 1 Month of Treatment With Elemental Diet (Postdiet)

	Prediet	Postdiet	<i>p</i>
Eosinophils/HPF	33.7 \pm 10.3	1.0 \pm 0.6	<0.01
Abdominal pain	40	2	<0.01
Vomiting	36	1	<0.01
Heartburn	27	2	<0.01
Water brash	11	1	<0.01
Globus	9	1	<0.01
Dysphagia	7	0	<0.01
Chest pain	4	0	0.04
Night cough	5	1	0.1
Irritability	3	0	0.08

HPF = microscopic high-powered field, equivalent to $40\times$.

The average time to clinical improvement was 8.5 ± 3.8 days. The diet was administered to three patients orally, and to 48 patients via nasogastric tube. For each patient diagnosed with EoE, the number of esophageal eosinophils/HPF in the distal esophagus was compared before and after treatment with the elemental diet. In addition, the number of patients experiencing symptoms was compared before and after treatment. All but two patients experienced improvement on the elemental diet. Responders did not differ from nonresponders by type of symptoms or degree of eosinophilia.

The number of eosinophils/HPF in the distal esophagus was significantly decreased after therapy with the elemental diet (Fig. 2). There were significant reductions in the number of patients experiencing the following symptoms: vomiting, abdominal pain, dysphagia, globus, heartburn, water brash, and chest pain. The number of patients experiencing night cough and irritability also decreased after the diet, but did not meet statistical significance. These results are summarized in Table 2.

Of the 51 patients diagnosed with EoE, visual inspection of the esophagus revealed 21 patients (41%) with evidence of esophageal furrowing (irregular, linear grooves in the esophageal mucosa). Thirteen patients (25%) had histologic evidence of eosinophilic abscess formation (defined as a collection of eosinophils on the surface of the esophageal mucosa). Patients with EoE were compared with the remaining 281 patients with regard to esophageal eosinophils, esophageal furrowing, and eosinophilic abscess formation (Table 3). Clinical symptoms, esophageal eosinophils/HPF, and response to diet did not vary when stratified by age and by sex.

Table 3. Comparison of Patients With EoE and Patients With GERD

	EoE Patients (51)	GERD Patients (292)	<i>p</i>
Eosinophils/HPF	33.7 \pm 10.3	2.1 \pm 0.8	<0.01
Furrows	21	101	ns
Eosinophilic abscess	13	0	<0.01

HPF = microscopic high-powered field, equivalent to $40\times$.

DISCUSSION

Before 1980, the histologic hallmarks for reflux esophagitis included basal zone hyperplasia, elongated papillae, and the presence of intraepithelial neutrophils (2–5). In 1982, the presence of intraepithelial eosinophils was suggested as an added criterion for the diagnosis of reflux esophagitis in children (6). This was later confirmed in adults (7). However, over the last 25 yr, several reports identified patients with a severe EoE not responding to standard antireflux therapy (8–11). The diagnosis of EoE has become extremely important as these patients are often misdiagnosed as having severe GERD and may undergo unnecessary antireflux surgery or may be committed to chronic use of antireflux medications without improvement of their esophagitis.

Idiopathic EoE, primary EoE, allergic esophagitis, and esophageal eosinophilia are several terms that have been used in the past to describe an isolated eosinophilia in the esophagus that cannot be attributed to GERD, parasitic infection, or other causes. The clinical features of EoE in children are often difficult to distinguish from children with GERD. The majority of patients with EoE present with a combination of chronic epigastric or substernal pain, vomiting, regurgitation, and nausea (9). Other associations include dysphagia, growth failure, hematemesis, globus, and water brash (11, 12). Stricture formation is a well-described entity in EoE (13–15), whereas extraintestinal manifestations, especially asthma, eczema, and chronic rhinitis, occur frequently in children (16).

There have been several reported treatments for EoE. In 1995, Kelly *et al.* (17) first described the effective use of an elemental diet in a small group of patients diagnosed with EoE. The authors studied a cohort of children with persistent symptoms of GERD not responding to various antireflux therapies, including histamine-2 receptor antagonists, prokinetic agents, and a Nissen fundoplication (17). Each was also noted to have increased numbers of eosinophils on endoscopic esophageal biopsy (median 41 eosinophils/HPF). Ten of these children underwent treatment with an amino acid-based elemental formula for a minimum period of 6 wk. Eight of 10 subjects had complete resolution of symptoms, whereas the remaining two had improvement. Follow-up endoscopy revealed significant improvement in the number of esophageal eosinophils (median 0.5 eosinophils/HPF). Symptoms recurred in nine of 10 patients after systematic food challenge. Avoidance of the offending foods allowed eight of 10 subjects to remain asymptomatic without antireflux medications.

Subsequently, alternative therapies including systemic and inhaled corticosteroids and enteral cromolyn sodium have been administered to patients with EoE. Liacouras *et al.* studied 20 patients with EoE, with persistent symptoms despite therapy with proton pump inhibitors, and showed that therapy with oral corticosteroids improved both the symptoms of EoE as well as the number of esophageal

intraepithelial eosinophils (9). The majority of patients developed a recurrence of symptoms upon discontinuation of the therapy.

In 1998, Faubion *et al.* reported that topical corticosteroids, administered from a metered-dose inhaler and then swallowed, also led to rapid, symptomatic improvement in four children with EoE (18); however, long-term follow-up was not established. More recently, Teitelbaum *et al.* demonstrated histologic and immunopathological results in patients with EoE treated with swallowed fluticasone propionate (19). These patients had a better response than patients placed on selective dietary restriction did, with restriction based on the results of allergy testing. This study is of special importance because it demonstrates that simply restricting foods, without the use of elemental diet, may be ineffective for treating EoE. Finally, there is anecdotal experience that oral cromolyn sodium may be useful in treating EoE. Although enteric cromolyn sodium has been used in children with eosinophilic gastroenteritis (20, 21), there have been no discreet studies with regard to EoE.

Despite the acceptance of EoE as an entity distinct from reflux esophagitis, there remains considerable ambiguity in both the criteria used to establish the diagnosis and in its treatment. Over the past 5 yr, many studies have attempted to characterize patients or demonstrate treatment of patients with EoE without adhering to a strict definition of EoE or without ascertaining information regarding histology or gastric acid. In addition, reports of EoE often included patients with eosinophilia of the stomach and intestine as well (15, 22–24). A recent series detailing EoE in children demonstrated many of the difficulties in establishing a definitive diagnosis (11). In this series, subjects were considered to have EoE if they had greater than five eosinophils/HPF (although the series was then stratified into those with five to 20 eosinophils/HPF and those with greater than 20 eosinophils/HPF). There was also considerable variability in the sites biopsied for diagnosis, the sites of the GI tract affected by eosinophilia, the presence or absence of food allergy, and the response to therapy.

Our study represents the largest trial of elemental diet in patients diagnosed with EoE to date. Although the main goal of this study was to demonstrate the therapeutic response of patients with EoE to an elemental diet, another goal was to better define EoE. Specifically, we hoped to classify the population as one distinct from those who suffer from eosinophilic gastroenteritis by limiting our population to those with only esophageal infiltration. We found that approximately one in seven patients identified with refractory reflux symptoms on histamine-2 receptor antagonists had an isolated esophageal eosinophilia with greater than 20 eosinophils/HPF. When GERD was excluded as a plausible explanation by pH probe monitoring, a subset of patients remained whom we believe exemplify the true entity of EoE. We also used the lack of response to proton pump inhibitors and a normal upper GI series as necessary criteria for inclusion. We believe that these criteria have allowed us

to differentiate EoE from other disorders. This method may also serve as an algorithm for diagnosing future patients with EoE.

Identification of patients with EoE was followed by a strict elimination diet. The response to the diet was overwhelmingly positive, with significant reductions in symptoms within 10 days, as well as a dramatic reduction of the number of eosinophils infiltrating the esophagus. The dietary trial period was 4 wk demonstrating that a long treatment course is not necessary to induce remission.

A limitation to this study was the interview process used. Although a standardized set of questions was used to assess symptoms, there was not a single person responsible for administering the questions or recording the responses. Additionally, some ambiguity may arise when differing responses are given from parents and children, with the potential for the most favorable response to be recorded. Because physicians were not blinded to therapy, there may have been a degree of bias in the recording of symptoms at the follow-up visit. Nevertheless, there was dramatic improvement in objective findings that could be considered less prone to bias, such as vomiting and the histologic findings. The biggest obstacle in this study was the method used to deliver the diet. Because the formula was unpalatable, most of the patients did not ingest it orally, opting instead for nasogastric administration. Initially, the prospect of nasogastric feedings was distressing to the families. However, the chronicity and severity of symptoms in the patients, combined with in-depth discussion regarding the potential side effects of long-term corticosteroid use was convincing to the families that a trial of elemental feeds was warranted. The rapid response to therapy further reinforced the acceptance of the diet, resulting in no patients discontinuing the feeding regimen.

Once EoE is diagnosed and treated with dietary elimination, the major difficulty lies in determining the patient's specific food allergens. EoE does not seem to be a strict IgE-mediated allergy (25). Instead, the cause of EoE may be a combination of IgE-mediated antibodies and T_H1-mediated reactions. Prior reports of EoE and eosinophilic gastroenteritis have used food allergy testing of all types to varying degrees, making interpretation of their role in diagnosis and treatment difficult. Similarly, elevated peripheral blood eosinophil count has had poor sensitivity and specificity for diagnosing EoE. Thus, although there are multiple methods available to test for food allergy, including radioallergosorbant testing, skin prick testing, and skin patch testing, no single test has yet to be distinguished as the best test to identify food allergens in patients with EoE. Currently, our method of choice is the slow reintroduction of single foods every 5 to 7 days while simultaneously observing clinical symptoms. Whenever ambiguity arises, repeat endoscopy with biopsy is performed.

The use of an elemental diet for EoE offers advantages over other reported therapies. Systemic corticosteroids, although proven effective, have well-known side effects,

which make their long-term use undesirable (26). Although topical (inhaled) corticosteroids may have a more acceptable perceived side-effect profile, they still carry potential side effects. Even when used in a small series of patients, esophageal candidiasis has been demonstrated with these medications (19). Additionally, there are some who question their effects on growth in pediatric patients (27–29). A third issue regards the long-term safety and efficacy of these agents when intentionally ingested—a manner of administration other than what was originally intended.

More importantly, corticosteroids or other anti-inflammatory agents, such as the mast cell stabilizer cromolyn, treat the final manifestation of the eosinophilic infiltration without addressing the primary cause. We believe that therapies that address and treat the underlying cause of EoE are superior to those that treat symptoms alone. When used in combination with well-delineated diagnostic criteria, we conclude that elemental diet is not only effective but also the best treatment option.

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