



Conservative long-term treatment of children with eosinophilic esophagitis

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ABSTRACT

Background: Current treatments of eosinophilic esophagitis (EoE), including restrictive diets or glucocorticoids, provide only transient improvement. Proton pump inhibitor (PPI) use in EoE does not lead to histologic improvement; however, the long-term use of PPI on symptoms and prevention of complications has not been evaluated.

Objective: To evaluate the use of PPI as maintenance therapy in children with EoE.

Methods: Eosinophilic esophagitis was diagnosed based on initial endoscopic biopsies and persistent eosinophilic inflammation despite PPI therapy. Inclusion criteria included diagnosis of EoE and PPI use as primary maintenance treatment. Patients were excluded if they were treated with dietary or glucocorticoid therapy. Histologic evidence of inflammation as well as degree of subepithelial fibrosis at presentation was compared with most recent biopsies while receiving PPI therapy.

Results: Thirty-eight patients (30 males and 8 females; average age 6.7 ± 5.4 years) fulfilled inclusion criteria. Duration of follow-up was 3.0 ± 2.4 years. At presentation, vomiting was significantly more frequent in the younger patients, whereas dysphagia occurred more frequently in the older patients. At follow-up, 26 patients were asymptomatic, and the remaining 12 patients' symptoms were significantly improved. No complications of stricture or food impaction were seen. Significant eosinophilic inflammation persisted in 28 patients. No difference in degree of subepithelial fibrosis at diagnosis compared with most recent biopsies. The z-scores of the treated EoE patients significantly improved.

Conclusions: Patients with EoE treated with PPIs show an improvement in symptoms and z-scores despite persistent eosinophilic inflammation. PPI treatment may be useful maintenance therapy in children with EoE.

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Introduction

Eosinophilic esophagitis (EoE) is an increasingly recognized disorder characterized by eosinophilic inflammation and clinical symptoms of esophageal disease. Children may present with a spectrum of symptoms, including frequent regurgitation, vomiting, abdominal pain, heartburn, dysphagia, chest pain, food intolerance, and food impaction.^{1–3}

Eosinophilic esophagitis has distinctive endoscopic and histologic features. On gross inspection by endoscopy, common findings characteristic of EoE are rings with strictures, linear furrowing, erythema, edema, corrugation, nodularity, and plaques that consist of eosinophilic microabscesses.⁴ A subset of patients may have an unremarkable endoscopy with normal-appearing mucosa but demonstrate histologic features of EoE on biopsy.⁵ The gold standard for the diagnosis of EoE is endoscopy, with biopsy specimens of

the esophagus demonstrating infiltration of the esophagus with eosinophils. Biopsy findings of an increased number of eosinophils per high-power field (HPF) are characteristic of EoE, with a cutoff of >15 eosinophils/HPF most commonly used.⁶ For the diagnosis of EoE, these findings are present in the absence of pathologic gastroesophageal reflux as evidenced by a normal pH monitoring study of the distal esophagus or a lack of response to proton-pump inhibitors (PPI).

Current medical therapies for EoE include topical or systemic corticosteroids,^{7–10} mast cell inhibitors, leukotriene receptor antagonists, and immune modulators.^{11,12} Dietary or environmental exposures often contribute to EoE. Patients are often referred for food allergy testing and placed on restrictive or elemental diets.^{13,14} Each of these treatments has its limitations and side effects. Furthermore, despite a temporary improvement in symptoms and histology, patients often rebound in symptoms and pathologic findings on endoscopy upon discontinuation of treatment.

The natural history of untreated EoE in the pediatric population is not entirely established. Untreated EoE is thought to lead to esophageal remodeling, progressing to esophageal dysmotility

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ity, strictures, scarring, and food impaction. The effect of treatment of EoE has been studied only in the context of short-term outcome. This natural progression of EoE has not been fully demonstrated in the pediatric population.

The use of PPIs does not lead to histologic improvement in patients with EoE.¹⁵ However, symptomatic improvement has been noted in children on PPI therapy. The aim of our study was to evaluate the use of long-term PPI treatment as maintenance therapy in children with EoE.

Methods

A historical pre–posttreatment study design was performed based on a chart review of patients who were diagnosed with EoE at Cohen Children's Medical Center from January 1995 to December 2009. Patients who had at least 2 endoscopies with a histologic diagnosis of EoE were included in the study. Inclusion criteria included diagnosis of EoE based on symptoms and initial endoscopic biopsy specimens demonstrating greater than 15 eosinophils/HPF. In addition, all patients had persistent eosinophilic inflammation on subsequent endoscopy despite treatment with PPIs. Patients were evaluated by an allergist for evidence of allergy to relevant dietary antigens or to aeroallergens. Skin prick testing was performed with commercial extracts (Alk Abello, Round Rock, Texas) on the forearm or back via the Multitest device (Lincoln Diagnostics, Decatur, Illinois), using positive histamine and negative saline controls. The largest diameter of the wheal and flare was measured at 20 minutes, with a positive result defined as a wheal greater than 5 mm larger than the negative control.

Atopy patch tests to food were also performed according to methods described elsewhere.¹⁶ Patients were excluded from the study if they were treated with dietary therapy. Patients were also excluded from the study if they were treated with topical or systemic corticosteroids. Patients were continued on proton pump inhibitors as maintenance therapy.

Demographic and anthropometric data were collected, including age, sex, symptoms, treatment prescribed, z-scores, and peripheral blood eosinophil count at presentation and most recent outpatient visit. Endoscopic histology was compared from presentation to most recent endoscopy. In addition to histologic evidence of inflammation and numbers of eosinophils/HPF, the degree of esophageal subepithelial fibrosis was determined by assessing the extent of lamina propria collagen deposition, using trichrome staining.¹⁷ Clinical assessment at each follow-up clinic visit was done by the same physician (J.L.); in addition, patients' reporting of symptoms was recorded as well. Clinically, patients were characterized as being asymptomatic if their symptoms had completely resolved, symptomatic but improved if they had improvement but still intermittent complaints, and they were listed as having no improvement if their symptoms were unchanged (or worsened) after treatment with PPIs. Comparison of results between presentation and most recent endoscopy was done using paired *t* test. Fisher's exact test was used to compare symptoms between older and younger EoE patients, with *P* < .05 considered significant.

The study was approved by the Institutional Review Board of the North Shore/LIJ Health System.

Results

Forty-seven patients met inclusion criteria for EoE (average age, 6.4 ± 5.3 years; 38 males). Of the 47 patients, 6 had been placed on dietary restrictions, and 3 had received corticosteroids. The remaining 38 patients were included in the study. Of the 38 patients studied, the average age at presentation was 6.7 ± 5.4 years (median, 5.1 years), with 30 males and 8 females.

All patients had 2 or more endoscopies. The average number of endoscopies performed was 3.7. The interval between endoscopies

Table 1

Demographic and clinical data

Total patients	38	
Male	30	
Female	8	
Age at presentation	6.7 ± 5.4 years	
Duration of follow-up	3.0 ± 2.4 years	
Presenting symptoms	<5.1 years (N = 19)	>5.1 years (N = 19)
Vomiting	8 ^a	1
Reflux	2	1
Dysphagia	1	8 ^a
Abdominal pain	1	4
Poor weight gain	4	1
Choking	1	1
Chest pain	0	3
Unexplained anemia	2	0

^a*P* < .05.

was determined by the treating clinician based on clinical findings. Duration of follow-up was 3.0 ± 2.4 years.

The most common presenting symptoms reported in children with EoE were dysphagia and vomiting (each 8 of 38, or 21%). Other reported symptoms included reflux, abdominal pain, chest pain, choking episodes, poor weight gain, and unexplained anemia. Based on the 50% age at presentation of 5.1 years, symptoms in the children older than 5.1 years were compared with those who were younger than 5.1 years at diagnosis. Dysphagia was seen significantly more frequently in the older patients, and vomiting was significantly more common in the younger patients with EoE (*P* < .05). No significant difference was seen in other presenting symptoms between the older and younger children with EoE (Table 1).

Eleven of the 38 patients underwent allergy testing, with 4 of 11 patients testing positive to food antigens (One patient reacted to fish, shellfish, tree nut, and stringbean; 1 reacted to egg white; 1 reacted to egg white, strawberry, rice, and watermelon; and a fourth patient reacted to peanut, walnut, and soybean). Three of 4 patients were found to have environmental allergies (3 to dust mite, 2 to cat dander, and all 3 to pollen). Atopy patch tests to foods were performed in 4 patients. Three patients tested negative to a panel of 24 foods; 1 patient had equivocal patch test results to soy and oat.

All 38 patients were treated with proton pump inhibitors (27 lansoprazole, 11 omeprazole). The starting dose of PPI therapy was 1.2 ± 0.6 mg/kg/day. Nine patients were also treated with ranitidine at some time during their follow-up period (5.0 ± 1.5 mg/kg/day). Additional medications received by the patients' during the follow-up period included Propulsid (3 children), Ritalin (1 patient), and Singulair (3 patients). The follow-up results are shown in Figure 1. At time of follow-up, 26 patients were asymptomatic. The remaining 12 patients reported their symptoms as significantly improved on PPI. No patients reported worsening or no improvement of symptoms. Of the 26 patients who reported that their symptoms had resolved, 20 continued to have eosinophilic inflammation with greater than 15 eosinophils/HPF on endoscopic biopsy. Of the 12 patients who reported occasional symptoms, 8 patients had greater than 15 eosinophils/HPF, and 4 patients had fewer than 15 eosinophils/HPF on their most recent esophageal biopsy. No complications of stricture or food impaction were seen.

No difference was found in the degree of subepithelial fibrosis as determined by extent of collagen deposition from the biopsies from the EoE patients at diagnosis compared with the biopsies obtained from the most recent endoscopy (*P* = .67).

Peripheral blood eosinophil count at presentation was 0.62 ± 0.4 K/ μ L and at most recent follow-up was 0.39 ± 0.3 K/ μ L (*P* = .11; normal, 0.0–0.5 K/ μ L).

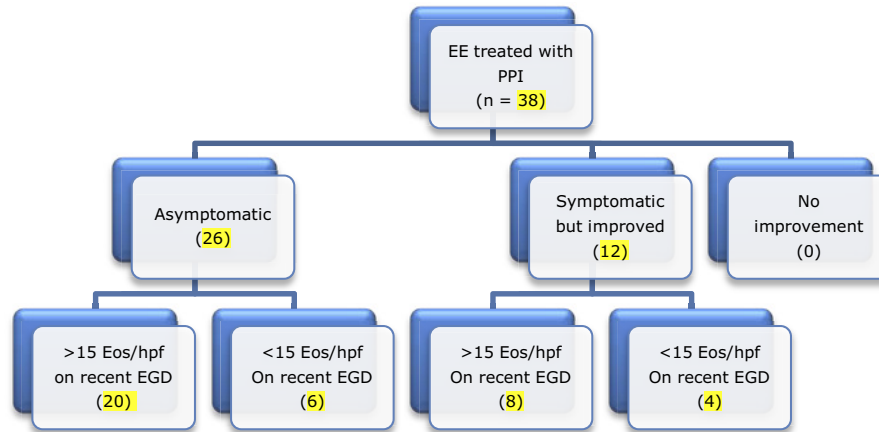


Figure 1. Follow-up of EE patients on PPI therapy.

The z-scores of the treated EoE patients significantly improved from -0.143 ± 1.1 at presentation to 0.082 ± 1.1 at follow-up ($P < .05$).

Discussion

This study describes 38 pediatric patients diagnosed with EoE and treated conservatively with PPI monotherapy. In our group of children with EoE treated with PPIs, we noted an improvement in symptoms over time, although often without histologic resolution of esophageal eosinophilia. Among the long-term side effects of EoE is esophageal strictures; this is thought to be attributable to increased collagen deposition with subepithelial fibrosis. In our patients, we did not find any increase in fibrosis while on PPI therapy, despite persistent eosinophilic inflammation.

Increasing evidence indicates that chronic inflammation is an important mediator of growth failure in children and that this effect is mediated through different mechanisms than those associated with steroid therapy and malnutrition.^{18–20} However, whether chronic esophageal inflammation in patients with eosinophilic esophagitis leads to growth impairment is unknown. Being that most of our PPI-treated patients continue to have esophageal inflammation, we were concerned that this inflammation may affect growth. Our study demonstrated that over the period of follow-up the Z-scores of our EoE patients treated with PPIs increased despite the persistent inflammation. In addition, long-term use of PPI may have less risk regarding growth compared with some of the other treatments being used in EoE patients.

The population of patients studied did not demonstrate an improvement in peripheral blood eosinophilia. A recent study has demonstrated that peripheral blood eosinophilia correlated with eosinophilic inflammation in the esophagus and may be used as a marker for histologic improvement in patients with EoE.²¹

Although several therapies are advocated as long-term treatment for EoE, no placebo-controlled studies have been performed in the pediatric population evaluating long-term effect on symptoms and complications. Konikoff et al²² reported a randomized, placebo-controlled trial of fluticasone as treatment of EoE, with a primary endpoint of histologic remission. Dohil et al²³ reported oral viscous budesonide to be an effective treatment of EoE based on histology and symptom score compared with PPI in a placebo-controlled study of 24 patients. The follow-up time was only 3 months. Although the improvement in mean symptom score was not statistically significant, 2 of 9 patients did report a resolution of symptoms. In our study, we have demonstrated that patients may have symptomatic remis-

sion without complications of EoE despite persistence of eosinophilia on biopsy.

Longer follow-up is needed to determine whether persistent EoE in PPI-treated patients is associated with any long-term complications. Whether the histologic changes of EoE in the pediatric population result in complications as patients enter adulthood is not known.

The weaknesses of this study include its retrospective nature, small sample size, and relatively short period of follow-up. Nevertheless, the data suggest that a prospective, randomized long-term evaluation of PPI as treatment and maintenance therapy for EoE in pediatric patients is warranted.

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