The natural history of steroid-naïve eosinophilic esophagitis in adults treated with endoscopic dilation and proton pump inhibitor therapy over a mean duration of nearly 14 years (CME)

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Background: Despite the vast focus of research in eosinophilic esophagitis (EoE), the natural history of untreated EoE remains undefined. Current expert consensus panels are calling for natural history studies to define long-term risks, adverse events, and progression of the disease.

Objective: To address the natural course and long-term adverse events of EoE.

Design: Retrospective, single-center study.

Setting: Tertiary-care center. A cohort of patients from the year 1988 initially diagnosed as having congenital esophageal stenosis who were later reclassified as having EoE.

Patients: Ninety-five patients, with 13 meeting entrance criteria for idiopathic EoE with follow-up >5 years.

Interventions: Anti-acids and esophageal dilation.

Main Outcome Measurements: Clinical response, adverse events, long-term clinical outcomes, and progression of disease.

Results: Thirteen patients (mean age at diagnosis 30.3 years, 10 male) were evaluated over a 13.6-year mean follow-up (range 5-24 years). All patients experienced daily dysphagia, with 12 presenting with food impactions. Patients were treated with esophageal dilation (64% Maloney, 34% Savary, 2.5% through-the-scope balloon) and daily anti-acids. Patients were initially treated with an average of 3.2 dilations over the first year (range 1-6) to achieve a luminal size of 15.8 mm (range 14-18 mm). They were maintained successfully with dilations every 2 years, on average, based on symptoms. Two patients not adhering to recommended dilation schedules experienced repeat impactions. One adverse event from a mucosal tear required hospitalization (1 of 157, 0.6%). Seven of 13 had Barrett's esophagus, average length 2.4 cm (range 1-4 cm), 3 on initial EGD and 4 identified over a mean duration of 9.4 years. No patient developed dysplasia or malignancy.

Limitations: Retrospective, small sample.

Conclusion: The course of EoE over a 13.6-year mean duration, although persistent, appears benign and not associated with cancer risk. A program of regular esophageal dilations based on symptom recurrence appears to be a safe, long-term treatment. (Gastrointest Endosc 2014;80:592-8.)

(footnotes appear on last page of article)

Since inception of the term *eosinophilic esophagitis* (EoE) into the medical literature in 1978, the disease has evolved from sporadic case reports to a significantly recognized cause of morbidity, with an estimated prevalence of 43 to 55 cases per 100,000 persons in the adult population.[1-3] EoE is defined as a chronic, immune and/or antigen-mediated disease characterized by symptoms related to esophageal dysfunction and histologically by

eosinophil-predominant inflammation.[4] The disease can present in any age group from newborn to the elderly[5]; however, it is found most often in young to middle aged white men.[6]

The histology and phenotype of the disease was first described by Attwood et al[7] in 1993 and later by Straumann et al[8] in 1994. According to the second EoE consensus statement, EoE is a clinicopathologic diagnosis defined as *symptoms related to esophageal dysfunction, ≥15 eosinophils per high-power field, eosinophilia that persists after a trial of proton-pump inhibitor (PPI) therapy, and exclusion of other secondary causes of esophageal eosinophila.*[4] In children, symptoms are typically vague in nature, usually presenting as abdominal pain, failure to thrive, heartburn, and vomiting.[9] In contrast, the predominant symptoms in adults consist of dysphagia, food impaction, and ongoing symptoms of GERD refractory to treatment.[10,11]

Despite the increased perception and vast focus of research on EoE, the course of disease over time left untreated or natural history remains a relative mystery. This deficiency in information prevents clinicians from comparing any true benefit of current therapeutic recommendations against the otherwise natural course of the untreated disease. Only one study in the adult literature describes the natural history of EoE, which was prospectively collected over a mean duration of 7.2 years.[12] Likewise, the natural history in pediatric EoE is limited, relying on retrospective data to characterize the disease course over time.[13-17] The majority of evidence supports a common pathogenesis for EoE in adults and children.[18] Although the natural history is currently limited, patients are generally warned that symptom recurrence and chronic need for long-term dietary or anti-inflammatory treatment are likely. Whether long-term sequelae from chronic esophageal inflammation and progression of disease exists remains to be demonstrated through natural history studies.[4,19]

We enjoyed the unique experience of following patients who had met the current criteria for EoE since 1988. Dr H. Worth Boyce at the University of South Florida initially identified patients with a primary complaint of dysphagia and endoscopic findings compatible with EoE, that is, strictures, multiple rings, and generalized esophageal narrowing. He called this disease "congenital esophageal stenosis" because of the similarity to a known pediatric disease, which was associated with trachealization of the proximal to mid-esophagus resulting from tracheobronchial tissue lingering in the esophagus from incomplete separation of the fetal trachea and esophagus.[20] Dr Boyce kept detailed records of patient demographics, symptoms, treatment, adverse events, and endoscopic features of this disease, including biopsy results, which on subsequent review were consistent with EoE.[21] These patients were not treated with steroids but were managed with anti-acid therapy and esophageal dilation because the histologic findings

> **Take-home Message**
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> - The natural history of fibrostenotic eosinophilic esophagitis is a benign disease over a follow-up duration of up to 24 years.
> - Biennial esophageal dilation and proton pump inhibitors give excellent long-term symptom relief with very low rates of adverse events.

were interpreted at that time as chronic reflux disease, sometimes with excessive eosinophils. This cohort of patients offers the distinct opportunity to address the natural course and long-term adverse events of EoE when steroids are omitted.

METHODS

Sample population

Institutional review board approval was obtained from the University of South Florida and H. Lee Moffitt Cancer Center. Patients were selected from a database of patients diagnosed with congenital esophageal stenosis initiated in 1988 by Dr Boyce at the University of South Florida Joy McCann Culverhouse Center for Swallowing Disorders in Tampa, Florida. This is a predominantly white patient population found in an urban area of 2 million people located on the west coast of Florida. We reviewed the patient records of 95 patients from 1988 to 2013 diagnosed with congenital esophageal stenosis and/or EoE. Patient notes were assessed along with endoscopic reports. Biopsy reports from each endoscopic session interpreted as reflux esophagitis were sent for re-examination for diagnosis of EoE by a GI pathologist experienced with this disease. Over this period, most biopsy specimens were obtained from the distal esophagus, looking for Barrett's esophagus (BE) or progression to dysplasia, and selectively from ringed and/or stricture areas. Usually, 4-quadrant biopsy specimens were taken every 2 cm beginning just above the gastric folds and ending at the new Z line (range of 4-12 biopsies). Biopsies also were done on any focal mucosal abnormalities. Biopsies were not routinely done on the proximal and distal esophagus. Records of treatment and medications, including PPI/H2 receptor antagonist/steroid therapy and dilation, were collected for analysis. Results of patient dilations including esophageal lumen size, number of dilations, year of dilation, and adverse events were recorded for analysis.

Inclusion/exclusion criteria

Eligibility required chart documentation of dysphagia for solid foods with or without food impactions and endoscopic and/or histologic evidence of EoE. The general work-up for patients included ruling out other known causes of esophageal eosinophilia such as collagen vascular disease, autoimmune processes, or infections. Patients

were excluded if they had only 1 visit to the clinic (n = 50), a final diagnosis of GERD based on pH test or response to PPI therapy (n = 7), received steroids at any point (n = 11), or failed to demonstrate chart documentation of eosinophils on esophageal biopsy (n = 1). The 50 patients with one clinic follow-up were referred from practices within the southeast area, and they returned to their primary centers. The 11 patients receiving steroids all had a diagnosis of EoE made after the first EoE consensus report in 2007.[22] Additionally, we excluded 13 patients with <5 years of follow-up (3 patients with 3 years, 5 with 2 years, and 5 with ≤1 year) to focus on the natural history of disease over time. Final analysis was performed on the remaining 13 patients treated only with anti-acids and endoscopic dilation.

RESULTS

Table 1 shows the demographic characteristics of the 13 patients meeting inclusion criteria. Our study group was male-predominant and all from the white population. The mean age of presentation to the swallowing center was 30.2 years. The average age of initial manifestation of EoE was 19.2 years, with all patients reporting dysphagia before diagnosis and 92% experiencing food impaction before presentation. Other symptom presentations included GERD and chest pain, 54% and 15%, respectively. Three patients reported asthma, and 4 experienced food allergies (1 tuna/honey, 1 egg/dairy, 1 poultry, and 1 poultry/shellfish). The mean delay to diagnosis was 11.1 years. The mean follow-up for the 13 patients from initial clinic visit was 13.6 years (range 5-24 years).

Histologic review

We attempted to collect all histologic slides from 1988 to 2011 for review by a GI pathologist experienced in diagnosing EoE. Slides from 2 of our academic institutions were reviewed; however, slides from private histopathology laboratories could not be retrieved. Of the 2 sites from which slides were available, 1 institution had discarded all biopsy slides taken before 2000. Slides from 9 of the 13 patients were reviewed, meeting the histologic cut-off of >15 (range 20 to >100). Two charts from where slides were unavailable mentioned biopsy proven eosinophilic esophagitis; however, no count could be obtained. The other 2 patients' reports revealed numerous eosinophils, but no eosinophil count was documented.

Endoscopy

An average of 10 EGDs were performed over the course of treatment for each patient (Table 2). Before standard terminology for describing the inflammatory endoscopic features in EoE such as furrows, exudates, or eosinophilic abscess formation, Dr Boyce used the

TABLE 1. Demographic characteristics	
Sex, no. (%)	
Male	10 (76.9)
Female	3 (23.1)
Age, mean (range), y	
Age at diagnosis	30.3 (15-57)
At first symptom	19.2 (1-57)
At follow-up	43.8 (25-68)
Duration, mean (range), y	
Symptoms prior to diagnosis	11.1 (2-23)
Follow-up after diagnosis	13.6 (5-24)
Presenting symptoms, no. (%)	
Dysphagia	13 (100)
Food impaction	12 (92.3)
GERD	7 (53.8)
Chest pain	2 (15.4)
Personal history of allergic disease, no. (%)	
Asthma	3 (23.1)
Food allergies	4 (30.8)
Skin allergies	–
Drug allergies	5 (38.5)

terms *linear creases, plaques, mucosal nodules* and *pits* to describe findings in patients with congenital esophageal stenosis. All patients had 1 or more of these findings. Multiple rings were found on the initial EGD in 11 of 13 patients, with the majority recorded in the proximal esophagus (54%). Generalized narrowing was seen in 2 patients: 1 in the mid-esophagus and the other confined to the distal esophagus. Four patients had hiatal hernias (range 2-4 cm).

BE confirmed by the histologic presence of intestinal metaplasia was identified in 7 patients (Table 2); however, no one went on to develop dysplasia or malignancy. Three patients showed histologic evidence of BE on the initial EGD biopsy, with 4 developing BE over a mean duration of 9.4 years. The average BE segment length was 2.4 cm (range 1-4 cm).

Dilation and compliance

No patient received steroids before data collection. Treatment consisted of either H2RA (39%), PPI therapy (92%) or a combination in addition to esophageal dilation (Table 3). Patients were dilated with Maloney

TABLE 2. Endoscopic characteristics

EGD, average no. (range)	10 (3-35)
Multiple rings, no. (%)	
Proximal	7 (53.8)
Distal	2 (15.4)
Throughout	2 (15.4)
Narrowing, no. (%)	
Mid-esophagus	1 (7.7)
Distal esophagus	1 (7.7)
Hiatal hernia, no. (%)	4 (30.8)
Barrett's esophagus, no. (%)	
Total	7 (53.8)
On initial EGD	3/7 (42.9)
Over course of follow-up	4/7 (57.1)
Time to Barrett's esophagus after initial EGD, average, y	9.4
Length of Barrett's esophagus, average, (range), cm	2.4 (1-4)
Dysplasia	0
Malignancy	0

TABLE 3. Therapy and dilation characteristics

Therapy, no. (%)	
PPI	12 (92.3)
H2RA	5 (38.5)
Steroids	0 (0)
Dilations	13 (100)
Dilations, total no.	157
Dilation/patient, average (range)	12.1 (4-35)
Type of dilation, no. (%)	
Maloney	11/13 (84.6)
Savary	10/13 (76.9)
Through-the-scope balloon	2/13 (15.4)
Dilation	
Lumen size, initial, average (range)	10.9 (6-16)
Lumen size, end of 1st y, average (range)	15.8 (14-18)
Dilations in 1st y, average (range)	3.2 (1-6)
Dilations/y to maintain 17 mm lumen, no.	0.59
Adverse events, no. (%)	
Hospitalization	1 (0.6)
Perforation	0
Bleeding	0
Mortality	0

PPI, Proton-pump inhibitor; *H2RA*, H2 receptor antagonist.

bougies(85%), Savary-Guilliard bougies over a guidewire (77%), or through-the-scope balloons (15%). The average number of dilations per patient was 12.1, with 157 total dilations performed: Maloney (64%), Savary (34%), and through-the-scope balloons (3%). The average initial lumen size on presentation was 11 mm (6-16 mm) with a diameter of 16 mm (14-18 mm) established by the end of the first year. An average of 3.2 dilations were required the first year (acute induction phase) to achieve a 16-mm lumen size (Fig. 1). This diameter was maintained and slightly improved to an average size of 17 mm when dilation every 2 years was performed by using symptom recurrence to guide dilation (maintenance phase). Dysphagia resolved in all patients adhering to recommended follow-up, without further food bolus impactions and maintaining normal weight and regular diet.

Two patients not adhering to recommendations after initial serial dilations experienced repeat food impaction. One patient lost to follow-up for 4 years presented with a food impaction, chest pain, and esophageal perforation requiring thoracotomy. Subsequently, he remained symptom-free with dilation every 2 years. The second patient was initially dilated from 10 to 16 mm then lost to follow-up for 2 separate 3-year periods. These lapses resulted in food impactions with a pea and later steak. He received subsequent acute and maintenance dilation and was successfully observed for 9 years without adverse events with annual dilations.

One dilation resulted in a 3-day hospitalization for chest pain from an esophageal mucosal tear. There were no surgeries, perforations, bleeding, or mortalities out of the 157 total dilations.

DISCUSSION

We report the longest adult natural history study, 13.6 years (range 5-24 years), of patients with EoE to date, providing a unique, steroid-naïve experience unlikely to be replicated, with the latest EoE guidelines recommending corticosteroids as first-line therapy.[4,20] In our experience, fibrostenotic EoE appears to be a chronic, persistent disease that is symptomatically amenable to treatment with combination dilation and acid inhibition. This therapy allowed long-term symptom control and patient satisfaction with no adverse events when patients complied with our
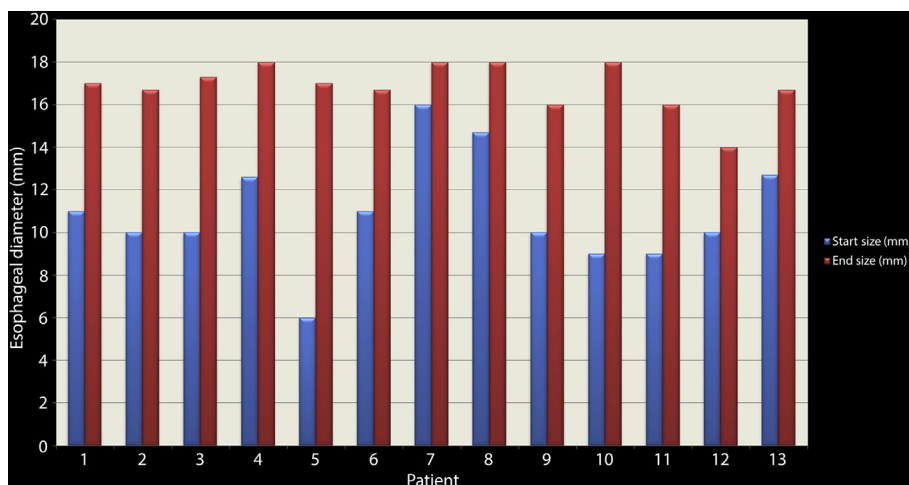
Figure 1. Change in esophageal diameter in 13 EoE patients treated only with esophageal dilation and anti-reflux therapy. On one presentation (blue), the initial esophageal diameter was 11 mm (range 6-16 mm). After the acute induction-phase dilations over the first year, the end mean esophageal diameter was 16 mm (range 14-18 mm). The red shows the end maintenance-phase diameter, with an average size of 17 mm (range 14-18 mm) sustained with dilation every 2 years.

recommended follow-up. No patients experienced spontaneous resolution of disease, and all complained of intermittent recurrent dysphagia responding to esophageal dilation every 2 years on average. Mucosal eosinophils remained confined to the esophagus without spread to other areas of the GI tract. About half of our patients had endoscopic and histologic evidence of BE, although no patients developed dysplasia. We found EoE in our patient population to be a relatively benign disease, with patients living normal, healthy lives without progressing to esophageal malignancy.

Since the first publication in 2003 by Straumann et al,[12] the natural history of EoE in adults remains largely undefined, with adverse events and long-term prognosis poorly understood. Expert consensus panels focused on EoE call for natural history studies to define long-term risks, adverse events, and progression of the disease.[4,20] The optimal natural history EoE study would prospectively enlist patients observed without treatment, which with modern-day medical and dietary options would be fundamentally unethical. Through Dr Boyce's careful profiling and record keeping of a disease unknown at the time, we were able to analyze a 13-patient cohort with nearly 14 years on average follow-up, range 5 to 24 years, generating this natural history study. Only anti-acid therapy was used because pathologists during this period were reading biopsy results of EoE as chronic inflammation due to GERD.

Studies in adult EoE patients suggest that inflammation and tissue remodeling over time varies among patients, defining 2 forms of the disease, with inflammatory and fibrostenotic phenotypes[23,24] According to endoscopic classification, whitish exudates, edema, and linear furrows constitute acute inflammation.[25] The fibrostenotic phenotype is associated with fixed rings, strictures, and a narrow

esophageal lumen.[23,24] Overall, 12 of our 13 patients presented with food impaction at the initial clinical visit. Multiple rings were seen in 85% of our patient population, and all of our patients were found to have strictures requiring dilations. Combined, these findings are compatible with an endoscopic fibrostenotic phenotype. Our patients had a delay in diagnosis of 11.1 years after initial presenting symptoms. This is comparable with Straumann et al,[12] where a delay of 4.6 years was reported, and a recently published study by Schoepfer et al,[26] in which an association between stricture formation and delayed EoE diagnosis was observed. The risk for fibrostenotic phenotype appears to double for every 10-year increase in age, suggesting that the natural history of EoE is a progressive disease.[27]

Despite evidence of cytokine and eosinophilic inflammation–induced tissue remodeling and fibrosis in EoE,[28] no study has determined the effect of dilation on the natural endoscopic course of the disease. Our experience indicates that after an initial acute induction stage, a near-normal esophageal diameter is sustainable with maintenance dilation every 2 years. One explanation may be that the initial tight fibrosis and collagen deposition are broken apart with induction-phase dilation, and dilations every 2 years promote remodeling of the esophageal lumen to a more acceptable diameter. This may explain why the 2 patients lost to follow-up required induction-phase dilations again but were amenable to maintenance dilation thereafter. Future studies focusing on EGD characteristics of patients undergoing esophageal dilation over time with histologic correlation may better delineate this observation.

Although inflammatory EoE responds well to corticosteroid therapy,[29,30] the role of corticosteroids in treating fibrostenotic disease is less well-documented. Long-term

steroid therapy may be necessary to decrease fibrotic scarring in adult EoE patients. This was suggested by Straumann et al[31] in a 54-week trial of the topical preparation budesonide 0.25 mg twice daily, in which 64% of patients were in clinical remission and biopsy and/or EUS showed less submucosal fibrosis. However, long-term steroid use, even if only swallowed, has potential adverse effects[32,33] and is a substantial financial burden. One review estimated a 6-week course of fluticasone at $740, whereas esophageal dilation without adverse events was $840.[34] Similar to several other studies, prolonged symptom relief after dilation to 15 to 18 mm was achieved in our patient group with an average dilation rate of every 2 years.[35,36] Thus, serial esophageal dilation over chronic steroid use provides more predictable symptomatic relief and may be a cost-effective method to treat fibrostenotic EoE in a disease with an overall benign long-term prognosis.

Savary-Guilliard or Maloney bougies were the dilators of choice in our population because of ease of utility, cost, and because they allowed passage of bougies throughout the entire length of the esophagus, where multiple strictures are often present. After assessing the size of the esophageal lumen on EGD, endoscopists used a smaller bougie, progressively increasing bougie diameter until 15 to 18 mm diameters were obtained. This is compatible with the recommended lumen diameter of 15 mm, allowing patients to eat a modified regular diet, and a diameter of 18 mm allowing a full regular meal.[37] Generally, progression of the bougie diameter each session was ≤3 mm after initial resistance, compatible with other reports.[35,38] Most patients were adequately dilated over ≤3 sessions, usually separated by 3 to 4 weeks. Post-dilation endoscopy to monitor for mucosal tears was not performed. Post-dilation pain was managed successfully with analgesics (rarely narcotics), resolving within a few days. In our study, no patients experienced perforation or required surgery. This is consistent with a recent review showing that among 525 EoE patients treated with nearly 1000 dilations, there were only 3 esophageal perforations, a rate of 0.3%, comparable to the non-EoE population.[39] Our study also highlights the importance of cautioning patients that dilation does not cure the disease, to expect some degree of recurrence of stenosis over time, and to be aware of the dangers of repeat food bolus impaction or esophageal perforation occurring if regular serial dilations are not maintained.

Spechler et al[40] suggested the possibility of a complex interaction between EoE and GERD—whether this extends to an association between BE and EoE has not been defined. It is not uncommon for patients with EoE to have concomitant BE, with several reviews reporting a prevalence ranging from 8.3% to 16%.[20,24,25,27,41] About half of our patients had endoscopic and histologic evidence of BE, although no patient went on to develop dysplasia or malignancy. Dr Boyce routinely performed a biopsy of the esophagogastric junction in his congenital esophageal stenosis patients secondary to the unknown

nature of this disease, perhaps explaining our high prevalence of BE. Whether surveillance screening in EoE patients should be performed remains to be determined.

Limitations of our study include a small patient sample of 13 patients, but this group reflects a cohort of patients with well-documented EoE selected from a larger patient population to focus on the disease's natural history. Another limitation is the retrospective design. The criterion standard would be a cohort study of untreated EoE patients followed prospectively; however, this may not be ethically possible. A food-focused questionnaire was not administered, but diligent food histories were available from initial visits. Finally, all biopsy specimens were not available for review, so the course of the eosinophil count could not be trended with time. Despite these limitations, this represents one of the only adult natural history studies of EoE and currently has the longest average follow-up duration in the medical literature about adults, approaching 14 years.

CONCLUSION

The course of fibrostenotic EoE over a mean duration of 13.6 years, although persistent, appears to be benign and not associated with cancer risk or need for surgery. In the fibrostenotic phenotype, esophageal dilation with PPIs offers a reasonable option for long-term symptomatic disease control. The role of an aggressive food elimination diet and chronic corticosteroid therapy remains unproven in adults with fibrostenotic EoE. Patients should be counseled that this is a chronic disease and there is currently no cure but only control of symptoms. Our experience suggests that esophageal dilation and PPI therapy is safe in the fibrostenotic phenotype and that this course of treatment remodels the esophageal rings and strictures, thereby allowing for long-term relief of dysphagia.

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