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ESOPHAGUS

A Gap in Care Leads to Progression of Fibrosis in Eosinophilic Esophagitis Patients

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BACKGROUND & AIMS: **There are few data assessing disease progression in eosinophilic esophagitis (EoE) after diagnosis. We aimed to determine outcomes and assess for progression of fibrosis in patients with EoE with a gap in their regular care.**

METHODS: **In this retrospective cohort study of newly diagnosed patients with EoE, a "gap" in care was defined as ≥2 years without medical contact for EoE. For inclusion, a gap in care and both pre- and post-gap endoscopies were required. Patients with and without a gap were compared. Data were also compared in gap patients before the gap and after EoE care resumed, and progression of fibrosis and predictors were assessed.**

RESULTS: **Of 701 patients with EoE, 95 (14%) had a gap in care (mean time without care, 4.8 ± 2.3 years). Post-gap, 12% presented with food impaction requiring emergency evaluation. Compared with pre-gap, patients post-gap had higher endoscopic severity (2.4 vs 1.5; $P < .001$) and smaller esophageal diameters (11.0 vs 12.7 mm; $P = .04$). Strictures were more prevalent with longer gap time ($P < .05$ for trend). Each additional year of gap time increased odds of stricture by 26%, even after accounting for pre-gap dilation. Additionally, of 67 patients without pre-gap fibrosis, 25 (37%) had at least one fibrotic feature (stricture, narrowing, or requiring dilation) post-gap.**

CONCLUSIONS: **A gap in care of ≥2 years in patients with EoE was associated with signs of increased disease activity, and progression to fibrostenosis was noted, particularly with longer gaps in care. Because EoE can progress to fibrosis even after diagnosis, regular care in patients with EoE is required, perhaps at intervals <2 years.**

Keywords: Dilation; Eosinophilic Esophagitis; Fibrosis; Natural History; Outcomes; Stricture.

Eosinophilic esophagitis (EoE) is an inflammatory and allergic disease of the esophagus that impacts people of all ages and is characterized by eosinophilic infiltration of the esophagus leading to symptoms of esophageal dysfunction.[1] Natural history studies suggest that in most patients, increasing symptom length prior to diagnosis, sometimes called "diagnostic delay," leads to higher prevalence of strictures or fibrostenosis when EoE is ultimately diagnosed.[2,3] This diagnostic delay has led to a model of disease progression when many, although not all, patients may transition from an inflammation-predominant picture (often manifested by edema, furrows, and exudates on endoscopy) to one of fibrostenosis (demonstrated by rings, strictures, and/or narrowing on endoscopy).[4] When this happens, esophageal dilation is often required to improve symptoms of dysphagia. Because EoE is a chronic disease, it requires ongoing maintenance treatment and monitoring with endoscopy to assess disease activity.[5,6] However, there are not yet set guidelines regarding clinical monitoring, and the lack of data on this topic makes recommendations for monitoring and surveillance intervals more difficult.

There are also few data assessing progression of disease for patients who do not have regular care. Two recent randomized withdrawal trials[6,7] and a prospective extension of a trial[8] showed that when treatment is

Abbreviations used in this paper: aOR, adjusted odds ratio; CI, confidence interval; EoE, eosinophilic esophagitis; hpf, high-powered field; PPIs, proton pump inhibitors.

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stopped, EoE disease activity nearly universally recurs, confirming data from a prior withdrawal study.[9] Cohort studies also suggest this.[10,11] However, progression was not specifically assessed in these prior studies, and because these studies were also relatively short-term, progression may not have been observed. The concept of progression from the inflammatory to the fibrostenotic phenotype has also been demonstrated in a case series, but data were limited.[12]

Given the knowledge gap related to this topic, as well as the importance of studying progression of EoE in a real-world clinical context, we aimed to determine outcomes and assess for progression of fibrosis in patients with EoE with a gap in their regular EoE care. We hypothesized that patients who were out of active care after their diagnosis of EoE would be more likely to progress to fibrostenosis than those who maintained follow-up.

What You Need to Know

Background

Because eosinophilic esophagitis (EoE) is chronic, long-term maintenance treatment and ongoing monitoring of disease activity is needed. However, few data examine the probability of disease progression after EoE diagnosis.

Findings

A total of 14% of the EoE study population had a gap in care after diagnosis, defined as 2 or more years without medical contact for EoE. After returning to care, higher endoscopic severity and smaller esophageal diameters were noted. Strictures were more prevalent with longer gap time, with each additional year of gap time increasing the odds of stricture by 26%.

Implications for patient care

EoE can progress to fibrosis even after diagnosis, emphasizing the importance of regular follow-up to monitor disease activity. Based on these data, follow-up intervals at less than 2 years, and which include an endoscopic assessment, may be appropriate for many patients.

Methods

Data Source and Patients

We conducted a retrospective cohort study utilizing the University of North Carolina EoE Clinicopathologic database, which contains data on patients with EoE of all ages seen at our center. Details of the origins of this database and data collection methods have been previously described.[13–16] In brief, available data included patient demographics, diagnostic information, and clinical features (symptoms, concomitant atopic conditions, endoscopic findings, eosinophil counts, treatments, and outcomes) that were extracted from medical records. For this study, subjects were adults and children with an incident diagnosis of EoE per consensus guidelines[1,17–19] who also had at least 2 years of follow-up available.

Gap in Care, Outcomes, and Variables of Interest

A "gap" in care was defined a prioi to be a period of time of at least 2 years without medical contact for treatment of EoE. There were a number of reasons for this definition. First, the ideal follow-up time is an understudied area in EoE. Second, as there are no published guidelines or consensus recommendations for follow-up in EoE, specific time intervals in clinical practice are generally individualized to the patient. Third, at our center, patients are typically seen for endoscopy every 2 to 3 months to assess treatment changes or for esophageal dilation until the disease is felt to be in remission, and then are seen in clinic every 6 to 12 months, with surveillance endoscopies at 1- to 2-year intervals. Therefore, it would be distinctly unusual for a routine follow-up recommendation to be made for more than 2 years, either in the clinical setting or in endoscopy, and for a patient not to be seen within 2 years. Although ultimately an empiric decision, the "gap" length of $\geq$2 years in this study was based in this context. We recorded the total time of the "gap," and defined follow-up broadly to include any clinic visits, phone calls, endoscopies, or other form of clinical contact related to EoE. Finally, to be included in the "gap" analysis, EoE cases were required to have a gap in care as well as both a pre-gap and post-gap esophagogastroduodenoscopy, so that endoscopic changes of fibrostenosis could be noted.

The main outcomes for the study were endoscopic and histologic findings following the gap in care. Endoscopic features included presence of exudates, rings, edema, furrows, strictures, and narrowing; the need for dilation was also recorded. Because this study included patients diagnosed with EoE prior to the advent of the EoE Endoscopic Reference Score, we instead calculated a proxy endoscopic severity score for which data were complete. This score summed the presence of exudates, rings, edema, furrows, strictures (each graded on a dichotomous 0/1 scale; range 0–5, with higher scores indicated more endoscopic severity). For patients with strictures or narrowing who required dilation, the pre-dilation esophageal diameter (as recorded by the performing endoscopist) and the post-dilation diameter (defined by the final dilator size) were also noted. We also constructed a variable of interest termed "severe fibrosis," which we defined as narrowing, stricture, or dilation performed at the pre-gap endoscopy. This was

an attempt to highlight patients with the most prominent fibrotic findings and did not include the presence of rings given that rings were very commonly seen in the study sample, even at baseline. For histology, we assessed the peak eosinophil count (eosinophils per high-power field; eosinophils/hpf; hpf size = 0.24 mm^2) on esophageal biopsy. Histologic response was defined as a post-treatment eosinophil count of <15 eosinophils/hpf.[20,21] We also examined symptom response. Because this was a retrospective study, we were unable to use validated patient-reported outcome metrics, and instead recorded the patient global symptom response as reported in the medical record.

Statistical Analysis

We used summary statistics to describe the study population. Demographics, clinical characteristics, treatment, and procedural data were compared between patients with and without a gap at the time of their diagnosis of EoE. Means were compared with a 2-sample t test, and proportions were compared with a χ^2 test. Multivariate logistic regression was performed to determine features that were independently associated with having a gap. Covariates were selected for the model based on differences in the bivariate analysis as well as by features that could impact having a gap clinically. Then, after construction of the initial model, we used backwards elimination to remove covariates that were not informative with a change in estimate threshold of 10%. Next, data were compared among gap patients before the start of the gap and after EoE care resumed, in order to investigate pre- and post-gap endoscopic features, treatments, and response rates. We then calculated the prevalence of strictures by the duration of the gap in care. Finally, we assessed progression to fibrosis in the patients without pre-existing strictures, narrowing, or dilation ("severe fibrosis"), compared features between progressors and non-progressors, and assessed the impact of maintaining treatment in the patients who had a gap in care. All analyses were performed with Stata version 12 (College Station, TX). The study was approved by the University of North Carolina institutional review board.

Results

Patient Characteristics

We identified 701 patients with EoE who met inclusion for our study with follow-up after 2 years. Of these, 95 (14%) met the definition of a gap in care. The mean time out of care was 4.8 ± 2.3 years. The most common reasons for a gap included loss to follow-up (63%), never being contacted for follow-up (21%), plans to return as needed (11%), insurance difficulties (1%), and moving from the area and then returning (1%). The mean time between EoE diagnosis and the start of a clinical care gap was 1.0 ± 1.2 years. Compared with patients without a gap in care, those with a gap were more likely to be older at age of diagnosis (34 vs. 28 years; $P = .004$), white (91% vs. 81%; $P = .01$), and have insurance (91% vs. 82%; $P = .03$) (Table 1). Although patients with a gap were less likely to have exudates, edema, and furrows on esophagogastroduodenoscopy, rings, presence of strictures, and dilations were similar to patients without a gap at diagnosis. After multivariate analysis, patients with a gap were more likely to be white (adjusted odds ratio [aOR], 0.37; 95% confidence interval [CI], 0.18–0.81) and have insurance (aOR, 2.73; 95% CI, 1.31–5.67), and less likely to have edema (aOR, 0.37; 95% CI, 0.21–0.65) and furrows (aOR, 0.55; 95% CI, 0.34–0.90) on endoscopy (Supplementary Table 1).

"Post-gap" Presentation and Impact

Eleven patients (12%) presented post-gap with an esophageal food bolus impaction requiring emergent medical evaluation, and 46 (48%) met our definition of severe fibrosis post-gap. When compared with the pre-gap period, patients had worse endoscopic severity scores (2.4 vs. 1.5; $P < .001$) after the gap (Table 2). Patients post-gap also had smaller esophageal diameters (11.0 vs 12.7 mm; $P = .04$) and less ongoing treatment ($P < .03$) (Table 2). However, the proportion of patients with histologic response (26% vs. 31%; $P = .51$) and symptom response (26% vs. 21%; $P = .31$) was not significantly different between the 2 groups. A larger proportion of patients in the pre-gap period was on EoE treatment compared with the post-gap period (71% vs. 54%; $P = .03$). Those presenting with a food impaction post-gap were more likely to be male (100% vs 52%; $P = .01$) and not have insurance (73% vs 93%; $P = .03$), as compared with those presenting without a food impaction post-gap; all other clinical, endoscopic, histologic, and treatment parameters were similar between the groups (Supplementary Table 2).

Progression of Fibrosis and Treatment Response

Strictures were more prevalent with longer gap time periods ($P < .05$ for trend) (Figure 1). For example, for a gap of ≥2 and <4 years, 27% had strictures, but for a gap of ≥8 years, 62% had strictures. Each additional year of gap time increased odds of stricture by 26%, even after multivariate analysis accounting for those with dilation pre-gap (aOR, 1.26; 95% CI, 1.03–1.55).

Of 67 patients who had no severe fibrosis pre-gap, 25 (37%) had at least one severe fibrotic feature (stricture, narrowing, or requiring dilation) post-gap. The patients who progressed to severe fibrosis had longer gaps

Table 1. Characteristics at Diagnosis Between Gap and Non-gap Patients

	Patients with EoE with no gap in care (n = 606)	Patients with EoE with a gap in care (n = 95)	P^a
Age at diagnosis, *years*	28.1 ± 18.5	33.9 ± 18.5	.004
Children (age <18)	226 (37)	25 (26)	.04
Male	406 (67)	63 (66)	.90
White	487 (81)	86 (91)	.01
Insurance	494 (82)	86 (91)	.03
Atopic diseases			
Allergic rhinitis	281 (47)	40 (44)	.71
Asthma	148 (25)	30 (33)	.21
Food allergy	185 (32)	23 (28)	.60
Symptom length prior to diagnosis, *years*	8.1 ± 8.8	8.9 ± 10.5	.52
Symptoms			
Dysphagia	438 (73)	78 (82)	.05
Food impaction	201 (34)	31 (34)	.92
Heartburn	226 (38)	38 (42)	.70
Chest pain	71 (12)	11 (12)	.93
Abdominal pain	108 (18)	16 (17)	.92
Endoscopic findings			
Exudates	276 (46)	26 (27)	.001
Rings	305 (50)	55 (58)	.18
Edema	273 (45)	20 (21)	< .001
Furrows	430 (71)	49 (52)	< .001
Stricture	174 (29)	20 (21)	.12
Narrowing	105 (17)	20 (21)	.38
Crepe-paper	29 (5)	4 (4)	.80
Dilation performed	180 (30)	24 (25)	.40
Peak eosinophil count, *eos/hpf*	67.0 ± 46.6	68.1 ± 32.3	.83

Note: Data are presented as mean ± standard deviation or number (%).
EoE, Eosinophilic esophagitis; eos/hpf, eosinophils/high-powered field.
[a]Means are compared with *t* tests; proportions are compared with χ^2 tests.

compared with non-progressors (mean 5.4 vs. 4.2 years; $P = .03$). Progressors to severe fibrosis were also less likely to have histologic response compared with non-progressors (12% vs. 38%; $P = .02$), and although symptom response in progressors was lower, it was not statistically significant (8% vs. 26%; $P = .07$). Older age, rings, history of dilation (during prior procedures before the pre-gap endoscopy), and being off of any treatment were also associated with progression (Table 3). When looking at all signs of fibrosis, there were 38 patients with no rings, stricture, narrowing, or dilation on the pre-gap endoscopy. Of these, 20 (53%) had at least one of these features post-gap.

For the post-gap patients, 51 (54%) remained on some EoE treatment, with proton pump inhibitors (PPIs) most common. For those not maintaining treatment during the gap, endoscopic severity was worse (3.0 ± 1.7 vs 1.8 ± 1.6; $P = .001$), symptom response was lower (11% vs 29%; $P = .003$), histologic response was less common (16% vs 43%; $P = .004$), and severe fibrosis was more common (59% vs 39%; $P = .05$) (Table 4).

Discussion

EoE is a chronic condition that requires symptomatic, endoscopic, and histologic follow-up to ensure disease control.[22] There are currently no set guidelines for follow-up time, and follow-up duration is determined based on patient characteristics and their health care provider preferences and practice preferences, rather than on evidence-based recommendations. The goal of this study was to better understand the relationship between gaps in care and disease progression and health outcomes. In this study, 14% of patients with EoE had a gap of at least 2 years with a mean of almost 5 years. Patients who presented following a gap in care had signs of increased disease activity, including 12% who presented with food impaction requiring emergent medical care, and loss of esophageal caliber with increased need for dilation. Additionally, we demonstrated that the length of the gap was strongly associated with fibrosis. The odds of having fibrosis increased by more than 25% per year of gap in care, and strictures similarly increased,

Table 2. Comparison of Pre-gap and Post-gap Features (n = 95 Patients With EoE)

	Pre-gap features	Post-gap features	P[a]
Endoscopic features			
Exudates	17 (18)	37 (39)	.001
Rings	46 (48)	59 (62)	.02
Edema	20 (21)	39 (41)	.002
Furrows	40 (42)	56 (59)	.009
Stricture	18 (19)	34 (36)	.008
Narrowing	9 (9)	20 (21)	.02
Esophageal diameter, *mm*	12.7 ± 2.8	11.0 ± 1.9	.04
Dilation performed	24 (25)	36 (38)	.02
Dilation size achieved, *mm*	15.6 ± 2.8	13.4 ± 3.3	.01
Total ESS[b]	1.5 ± 1.3	2.4 ± 1.7	< .001
Peak eosinophil count, *eos/hpf*	51.5 ± 49.1	57.1 ± 58.3	.38
Responses			
Histologic response (<15 eos/hpf)	25 (26)	29 (31)	.51
Symptom response	25 (26)	20 (21)	.35
Treatments			
Any treatment	67 (71)	51 (54)	.03
PPI	43 (45)	40 (42)	.64
Topical steroids	28 (29)	9 (9)	< .001
Daily dose, *mcg*	720 ± 347	632 ± 352	.37
Food elimination diet	9 (9)	10 (11)	.78

Note: Data are presented as mean ± standard deviation or number (%).
EoE, Eosinophilic esophagitis; eos/hpf, eosinophils/high-powered field; ESS, endoscopic severity score; PPIs, proton pump inhibitors.
[a]Means are compared with *t* tests; proportions are compared with χ^2 tests.
[b]The ESS is the sum of the presence of the 5 features of exudates, rings, edema, furrows, and/or stricture.

with a probability of 27% with a gap of 2 to 4 years and a rate of 62% with a gap of 8 or more years. These findings have implications for the long-term care of patients with EoE after initial diagnosis and treatment.

The natural history of EoE has been increasingly studied and characterized. There is agreement that eosinophilic infiltration of the esophagus and symptoms, specifically dysphagia, have been found to persist in disease, although the severity of symptoms may vary over time.[4,5] Like with other inflammatory disorders, the initially reversible inflammatory changes become persistent, and eventually, largely irreversible. In EoE, persistent esophageal eosinophilia is thought to contribute to structural changes including fibrosis, strictures, loss of distensibility, and dysmotility, and this leads on ongoing clinical symptoms.[23] When EoE starts in childhood, it nearly universally persists until adulthood,[24] with ongoing symptoms.[25] Longer periods of time without treatment are associated with higher rates of fibrostenosis,[2,3] and if histologic disease activity is controlled, fewer esophageal dilations are needed.[26] Although dilation is typically the recommended treatment when strictures are present, anti-inflammatory treatments have been shown to improve esophageal caliber and compliance,[15,27] and a subanalysis from a recent clinical trial showed specific improvement in fibrostenotic features with an esophageal-specific formulation of fluticasone.[28]

With EoE as a chronic disease requiring long-term maintenance, the question of how frequently patients should be monitored is key. Current EoE treatment guidelines recommend initial treatment, including pharmacological treatment, diet modifications, and/or dilation.[29,30] Additionally, guidelines also suggest maintenance therapy to help maintain remission, but remain silent on monitoring intervals. In an extended study of the Swiss EoE Cohort, Greuter and colleagues found that higher doses and longer treatment duration with topical steroids was more likely to achieve remission in EoE,[10] but that study design did not allow comment on monitoring intervals. In another long-term follow-up study by Greuter and colleagues, relapse despite topical steroid use was frequent, which emphasized that ongoing monitoring was important to assess disease activity.[11] However, additional data are needed,

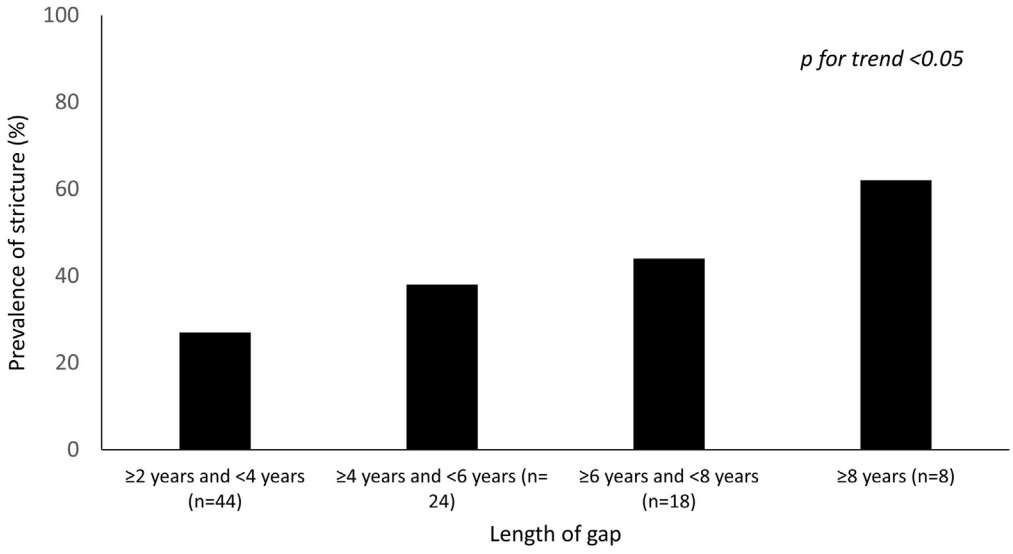

Figure 1. Increasing prevalence of stricture as the length of gap time without care increases.

Table 3. Characteristics of Patients With EoE Without Baseline Fibrostenosis Who Progressed to "Severe" Fibrosis, Defined as Stricture, Narrowing, or Dilation, at the Post-gap EGD

	Non-progressor (n = 42)	Progressor (n = 25)	P[a]
Age at diagnosis, *years*	26.6 ± 18.3	38.1 ± 18.3	.02
Children (age <18)	18 (43)	5 (20)	.06
Male	25 (60)	18 (72)	.30
White	35 (85)	24 (96)	.17
Insurance	38 (90)	24 (96)	.41
Atopic diseases			
Allergic rhinitis	21 (53)	9 (36)	.19
Asthma	13 (32)	7 (28)	.75
Food allergy	12 (32)	5 (22)	.37
Symptom length prior to diagnosis, *years*	6.1 ± 7.0	10.9 ± 13.0	.08
Symptoms			
Dysphagia	30 (71)	22 (88)	.12
Food impaction	11 (27)	11 (44)	.15
Heartburn	22 (54)	9 (36)	.16
Chest pain	6 (15)	3 (12)	.76
Abdominal pain	12 (29)	0 (0)	.003
Baseline endoscopic findings			
Exudates	11 (26)	8 (32)	.61
Rings	18 (43)	19 (76)	.008
Edema	9 (21)	4 (16)	.59
Furrows	21 (50)	14 (56)	.63
Stricture	2 (5)	3 (12)	.28
Narrowing	3 (7)	4 (16)	.25
Crepe-paper	1 (2)	0 (0)	.44
Dilation performed	2 (5)	6 (24)	.02
Baseline peak eosinophil count, *eos/hpf*	63.2 ± 34.3	74.9 ± 33.9	.19
Pre-gap endoscopic features			
Exudates	8 (19)	4 (16)	.75
Rings	14 (33)	15 (60)	.03
Edema	10 (24)	5 (20)	.72
Furrows	15 (36)	8 (32)	.76
Total ESS[b]	1.1 ± 1.2	1.3 ± 1.1	.58
Post-gap treatments			
Any treatment	26 (62)	9 (36)	.04
PPI	21 (50)	8 (32)	.15
Topical steroids	5 (12)	1 (4)	.27
Daily dose, *mcg*	884 ± 598	1760 ± 0	–
Food elimination diet	5 (12)	1 (4)	.27

Note: Data are presented as mean ± standard deviation or number (%).
EGD, Esophagogastroduodenoscopy; EoE, eosinophilic esophagitis; eos/hpf, eosinophils/high-powered field; ESS, endoscopic severity score; PPIs, proton pump inhibitors.
[a]Means are compared with *t* tests; proportions are compared with χ^2 tests.
[b]The ESS is the sum of the presence of the 5 features of exudates, rings, edema, furrows, and/or stricture.

Table 4. Outcomes at the Time of the "Post-gap" Endoscopic Evaluation, as Stratified by Ongoing EoE Treatments

	Not on treatment post-gap (n = 44)	On treatment post-gap (n = 51)	P[a]
Total ESS[b]	3.0 ± 1.7	1.8 ± 1.6	.001
Stricture present	25 (57)	36 (71)	.16
Narrowing present	13 (30)	7 (14)	.06
Dilation performed	19 (43)	17 (33)	.32
Esophageal diameter, *mm*	11.2 ± 3.6	10.2 ± 4.1	.47
Dilation size achieved, *mm*	13.2 ± 3.0	14.7 ± 2.5	.13
"Severe" fibrosis[c]	26 (59)	20 (39)	.05
Symptom response	5 (11)	15 (29)	.03
Peak eosinophil count, *eos/hpf*	74.9 ± 66.7	41.7 ± 45.3	.005
Histologic response (<15 eos/hpf)	7 (16)	22 (43)	.004

Note: Data are presented as mean ± standard deviation or number (%).
eos/hpf, Eosinophils/high-powered field; ESS, endoscopic severity score.
[a]Means are compared with *t* tests; proportions are compared with χ^2 tests.
[b]The ESS is the sum of the presence of the 5 features of exudates, rings, edema, furrows, and/or stricture.
[c]Defined as the presence of stricture, narrowing, or having dilation.

as none specifically look at monitoring intervals. As would be expected in this setting, clinical practice for EoE monitoring currently is variable. Some providers (as in the Swiss model[31]) would perform endoscopy annually, whereas others would monitor clinically and assess only symptoms, although this does not capture the entire spectrum of EoE disease activity necessary for response assessment. Most likely, the decision for monitoring intervals should be individualized to each patient based on symptoms, current disease activity, prior disease history (including food impactions and other complications, past growth or nutritional issues, requirement for prior or current dilation, and severity of esophageal strictures/narrowing), and patient preference. Patients with more severe features likely need closer follow-up. Based on data from our study data, however, a monitoring interval greater than 2 years may be too long for most patients with EoE, given the progression to fibrostenosis and lack on ongoing treatments. Within this time frame, it is notable that the same proportion of patients continued PPIs and diet elimination before and after the gap, but the use of topical steroids decreased substantially. Although the exact reason for the decreased steroid use cannot be determined from the present study design, it may be because PPIs are available over-the-counter and diet elimination can be done independently, but topical steroids require a prescription that requires ongoing follow-up in order for this medication to be continued.

There are limitations of our study to consider. First, it was a retrospective study conducted at a single academic center. Rates of stricture and dilation may be higher at our center compared with others, impacting the generalizability of our findings, but in general the

characteristics of the EoE population here are consistent with those reported at other centers. Similarly, there were more adults than children in this study (though one-quarter of the included patients were under 18 years), so these results may not apply to an exclusively pediatric population. This study used a nonvalidated global symptom assessment based on reporting in the medical record, given the retrospective design, so validated patient-reported outcome data are lacking. There were also no set prospective follow-up protocols, so clinician variability in determining follow-up intervals added heterogeneity, but this may also help the results apply to practice settings. Finally, our definition of "severe fibrosis" is not completely objective given that "narrowing" can be a subjective finding, and objective data such as provided by the functional luminal imaging probe were not available. Similarly, we did not have detailed histopathologic data available on lamina propria fibrosis, as this is not routinely available on clinical reports. Future prospective work should examine both of these more objective metrics of fibrosis. We also required a post-gap endoscopy so that fibrostenotic changes were captured, so the population is limited to those who returned to care, rather than those completely lost to follow-up. Our study also has multiple strengths. We implemented a cohort design with a large sample size and utilized detailed and granular data. Additionally, our data allowed for long-term follow-up, and our definition of a gap ($\geq$2 years) was strict and stated a priori. Finally, our study is the first of its kind to attempt to assess monitoring intervals and one of the first to study symptoms, histologic response, and endoscopic findings after a prolonged gap period with a subsequent return to care.

Conclusion

In conclusion, a gap in care of greater than 2 years in patients with EoE was associated with signs of increased disease activity, which presented as food impactions and worsening endoscopic features. A clear progression to fibrostenosis was also noted in this study, and this progression was more common with longer gaps in care. The data from this study show that EoE can progress to fibrosis even after diagnosis, and thus, the importance of regular follow-up to monitor disease activity clinically, endoscopically, and histologically. Based on this data, follow-up intervals at less than 2 years, and which include an endoscopic assessment, may be appropriate for many patients.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of Clinical Gastroenterology and Hepatology at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2021.10.028.

References

1. Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE conference. Gastroenterology 2018;155:1022–1033.e10.
2. Schoepfer AM, Safroneeva E, Bussmann C, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. Gastroenterology 2013; 145:1230–1236.e1–2.
3. Dellon ES, Kim HP, Sperry SL, et al. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. Gastrointest Endosc 2014;79:577–585.e4.
4. Dellon ES, Hirano I. Epidemiology and natural history of eosinophilic esophagitis. Gastroenterology 2018;154:319–332.e3.
5. Straumann A, Spichtin HP, Grize L, et al. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. Gastroenterology 2003;125:1660–1669.
6. Straumann A, Lucendo AJ, Miehlke S, et al. International EOS-2 Study Group. Budesonide orodispersible tablets maintain remission in a randomized, placebo-controlled trial of patients with eosinophilic esophagitis. Gastroenterology 2020; 159:1672–1685.e5.
7. Dellon ES, Collins MH, Katzka DA, et al, ORBIT2/SHP621-302 Investigators. Long-term treatment of eosinophilic esophagitis with budesonide oral suspension. Clin Gastroenterol Hepatol 2022;20:1488–1498.e11.
8. Dellon ES, Woosley JT, Arrington A, et al. Rapid recurrence of eosinophilic esophagitis activity after successful treatment in the observation phase of a randomized, double-blind, double-dummy trial. Clin Gastroenterol Hepatol 2020;18:1483–1492.e2.
9. Straumann A, Conus S, Degen L, et al. Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2011; 9:400–409.e1.
10. Greuter T, Safroneeva E, Bussmann C, et al. Maintenance treatment of eosinophilic esophagitis with swallowed topical steroids alters disease course over a 5-year follow-up period in adult patients. Clin Gastroenterol Hepatol 2019;17:419–428.e6.
11. Greuter T, Godat A, Ringel A, et al. Effectiveness and safety of high versus low dose swallowed topical steroids for maintenance treatment of eosinophilic esophagitis: a multi-center observational study. Clin Gastroenterol Hepatol 2021; 19:2514–2523.e2.
12. Koutlas NT, Dellon ES. Progression from an inflammatory to a fibrostenotic phenotype in eosinophilic esophagitis. Case Rep Gastroenterol 2017;11:382–388.
13. Reed CC, Corder SR, Kim E, et al. Psychiatric comorbidities and psychiatric medication use are highly prevalent in patients with eosinophilic esophagitis and associate with clinical presentation. Am J Gastroenterol 2020;115:853–858.
14. Reed CC, Fan C, Koutlas NT, et al. Food elimination diets are effective for long-term treatment of adults with eosinophilic oesophagitis. Aliment Pharmacol Ther 2017;46:836–844.
15. Runge TM, Eluri S, Cotton CC, et al. Outcomes of esophageal dilation in eosinophilic esophagitis: safety, efficacy, and persistence of the fibrostenotic phenotype. Am J Gastroenterol 2016;111:206–213.
16. Eluri S, Runge TM, Hansen J, et al. Diminishing effectiveness of long-term maintenance topical steroid therapy in PPI non-responsive eosinophilic esophagitis. Clin Transl Gastroenterol 2017;8:e97.

17. Furuta GT, Liacouras CA, Collins MH, et al. First International Gastrointestinal Eosinophil Research Symposium (FIGERS) Subcommittees. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. Gastroenterology 2007; 133:1342–1363.
18. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol 2011;128:3–20.e6.
19. Dellon ES, Gonsalves N, Hirano I, et al. American College of Gastroenterology. ACG Clinical Guideline: evidence-based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis. Am J Gastroenterol 2013;108:679–692.
20. Wolf WA, Cotton CC, Green DJ, et al. Evaluation of histologic cutpoints for treatment response in eosinophilic esophagitis. J Gastroenterol Hepatol Res 2015;4:1780–1787.
21. Reed CC, Wolf WA, Cotton CC, et al. Optimal histologic cutpoints for treatment response in patients with eosinophilic esophagitis: analysis of data from a prospective cohort study. Clin Gastroenterol Hepatol 2018;16:226–233.e2.
22. Dellon ES, Gupta SK. A conceptual approach to understanding treatment response in eosinophilic esophagitis. Clin Gastroenterol Hepatol 2019;17:2149–2160.
23. Hirano I, Aceves SS. Clinical implications and pathogenesis of esophageal remodeling in eosinophilic esophagitis. Gastroenterol Clin North Am 2014;43:297–316.
24. Ruffner MA, Brown-Whitehorn TF, Verma R, et al. Clinical tolerance in eosinophilic esophagitis. J Allergy Clin Immunol Pract 2017;6:661–663.
25. Menard-Katcher P, Marks KL, Liacouras CA, et al. The natural history of eosinophilic oesophagitis in the transition from childhood to adulthood. Aliment Pharmacol Ther 2013; 37:114–121.
26. Runge TM, Eluri S, Woosley JT, et al. Control of inflammation decreases the need for subsequent esophageal dilation in patients with eosinophilic esophagitis. Dis Esophagus 2017; 30:1–7.
27. Carlson DA, Hirano I, Zalewski A, et al. Improvement in esophageal distensibility in response to medical and diet therapy in eosinophilic esophagitis. Clin Transl Gastroenterol 2017;8:e119.
28. Dellon ES, Lucendo AJ, Schlag C, et al. Fluticasone propionate orally disintegrating tablet (APT-1011) improves histologic, endoscopic and symptom responses in eosinophilic esophagitis (EoE) patients with fibrostenotic features: results from a phase 2b randomized double blind placebo-controlled trial. Gastroenterology 2021;160(Suppl):S111–S112 (Abstract 540).
29. Hirano I, Chan ES, Rank MA, et al. AGA Institute Clinical Guidelines Committee; Joint Task Force on Allergy-Immunology Practice Parameters. AGA Institute and the Joint Task Force on Allergy-Immunology Practice Parameters Clinical Guidelines for the Management of Eosinophilic Esophagitis. Gastroenterology 2020;158:1776–1786.
30. Rank MA, Sharaf RN, Furuta GT, et al. , AGA Institute. Joint Task Force on Allergy-Immunology Practice Parameters collaborators. Technical review on the management of eosinophilic esophagitis: a report from the AGA Institute and the Joint Task Force on Allergy-Immunology Practice Parameters. Gastroenterology 2020;158:1789–1810.e15.
31. Greuter T, Bussmann C, Safroneeva E, et al. Long-term treatment of eosinophilic esophagitis with swallowed topical corticosteroids: development and evaluation of a therapeutic concept. Am J Gastroenterol 2017;112:1527–1535.

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Supplementary Table 1. Multivariate Analysis Results for Patients With and Without a Gap in Care

Covariate	Univariate result, OR (95% CI)	Multivariate result, OR (95% CI)
Age at diagnosis[a]	1.01 (1.00–1.03)	–
White race	0.39 (0.19–0.83)	0.37 (0.18–0.81)
Insurance	2.55 (1.05–4.41)	2.73 (1.31–5.67)
Dysphagia symptoms	1.71 (0.98–2.97)	–
Exudates on endoscopy	0.45 (0.28–0.73)	–
Edema on endoscopy	0.32 (0.19–0.54)	0.37 (0.21–0.65)
Furrows on endoscopy	0.43 (0.28–0.67)	0.55 (0.34–0.90)

CI, Confidence interval; OR, odds ratio
[a]OR is for an increase of 1 year.

Supplementary Table 2. Comparison of Post-gap Patients With EoE who Did and Did Not Represent With a Food Bolus Impaction

	No food impaction at presentation post-gap (n = 84)	Food impaction at presentation post-gap (n = 11)	P[a]
Age at diagnosis, *years*	34.5 ± 18.5	29.2 ± 19.0	.37
Children (age <18)	63 (75)	7 (64)	.42
Male	52 (62)	11 (100)	.01
White	75 (90)	11 (100)	.28
Insurance	78 (93)	8 (73)	.03
Atopic diseases			
Allergic rhinitis	35 (44)	5 (45)	.94
Asthma	25 (31)	5 (45)	.35
Food allergy	21 (28)	2 (22)	.70
Symptom length prior to diagnosis, *years*	8.8 ± 10.3	9.4 ± 12.3	.86
Symptoms			
Dysphagia	68 (81)	10 (91)	.42
Food impaction	26 (33)	5 (45)	.40
Heartburn	36 (45)	2 (18)	.09
Chest pain	10 (13)	1 (9)	.75
Abdominal pain	15 (19)	1 (9)	.44
Baseline endoscopic findings			
Exudates	23 (27)	3 (27)	.99
Rings	49 (58)	6 (55)	.81
Edema	19 (23)	1 (9)	.30
Furrows	43 (51)	6 (55)	.83
Stricture	18 (21)	2 (16)	.80
Narrowing	19 (23)	1 (9)	.30
Crepe-paper	4 (4)	0 (0)	.46
Dilation performed	21 (25)	3 (27)	.89
Baseline peak eosinophil count, *eos/hpf*	68.7 ± 32.7	61.8 ± 29.7	.56
Pre-gap endoscopic features			
Exudates	15 (18)	2 (18)	.98
Rings	41 (49)	5 (45)	.83
Edema	18 (21)	2 (18)	.80
Furrows	35 (42)	5 (45)	.81
Stricture	17 (20)	1 (9)	.38
Total ESS[b]	1.5 ± 1.3	1.4 ± 1.4	.74
Post-gap treatments			
Any treatment	44 (52)	7 (64)	.48
PPI	36 (43)	4 (36)	.68
Topical steroids	8 (10)	1 (9)	.96
Daily dose, *mcg*	945 ± 375	1000 ± 0	—
Food elimination diet	8 (10)	2 (18)	.38

Note: Data are presented as mean ± standard deviation or number (%).
EoE, Eosinophilic esophagitis; eos/hpf, eosinophils/high-powered field; ESS, endoscopic severity score; PPIs, proton pump inhibitors.
[a]Means are compared with *t* tests; proportions are compared with χ^2 tests.
[b]The ESS is the sum of the presence of the 5 features of exudates, rings, edema, furrows, and/or stricture.