

DISEASES OF THE ESOPHAGUS

Original article

Most children with eosinophilic esophagitis have a favorable outcome as young adults

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SUMMARY. The disease progression of eosinophilic esophagitis (EoE) from childhood into adulthood is unclear. To determine the clinical outcome of patients who were diagnosed with EoE as children, and who now are young adults. Children (<18 years old) diagnosed with EoE were enrolled in a prospective registry on demographics, presenting symptoms, and endoscopic/histologic findings. Subjects who now are adults (≥ 18 years old) were identified, and a structured telephone interview was conducted to obtain follow-up data on symptom prevalence (dysphagia to solids and liquids, nausea/vomiting, abdominal pain, and heartburn/regurgitation), food impaction, medication usage, health-care utilization, and resolution of atopy/food allergies. A favorable outcome was defined if EoE symptoms were resolved or improved by subjects' assessment. Unfavorable outcomes was defined as symptoms same or worse. Clinical variables that predicted a favorable outcome as an adult were examined. Mayo Dysphagia Scale (MDQ-30: scored 0–100) was administered to validate the outcome assessment. Mantel-Haenszel odds ratio and unpaired *t*-test were used. Fifty-eight subjects (64% male) who met study criteria were enrolled. Mean age at diagnosis was 12 years (range 4–17) and mean duration of follow-up was 8.3 years (2–16). As children, the most common presenting symptoms were abdominal pain (54%), dysphagia (33%), and vomiting (24%). As young adults, 47 subjects (81%) had a favorable outcome. Total MDQ-30 scores were 4.6 (0–30) and 14.1 (0–50) in subjects with favorable outcome and unfavorable outcome, respectively ($P = 0.015$). Two-thirds of subjects did not use steroids or proton pump inhibitors in the preceeding 12 months. Male children with EoE were four times more likely to have a favorable outcome as young adults compared with female children. Females were more likely to report nausea/vomiting as young adults (odds ratio 3.23, CI 0.97–10.60). Of all presenting symptoms in EoE children, dysphagia was the most likely to persist into adulthood (odds ratio 6.29, CI 1.85–21.38). Eighty one percent of EoE children had a favorable outcome as young adults. Most patients with symptom resolution did not require any form of steroid therapy or seek healthcare.

KEY WORDS: acid reflux, dysphagia, eosinophilic esophagitis, eosinophilic oesophagitis, eosinophils.

INTRODUCTION

Eosinophilic esophagitis (EoE) is characterized by eosinophilic infiltration of the esophageal epithelium and manifests clinically as esophageal dysfunction.¹ The prevalence of EoE has increased profoundly in Westernized countries in both children and adults over the last few decades.^{2–6} This is likely in part due to increased recognition by clinicians. While patients of any age may be diagnosed with EoE,^{7,8} it is well-

established that a patient's clinical presentation varies with their age at diagnosis.^{8,9} Adults often present with dysphagia for solids or food impaction whereas infants and children often present with a wider range of symptoms including abdominal pain, cough, nausea, vomiting, heartburn, or failure to thrive.^{8,9}

Although clinical and research interest in EoE has increased markedly over the last 10–20 years, our knowledge of the disease progression from childhood to young adulthood is limited.¹ Anecdotal clinical experience suggests that although some children continue to remain symptomatic into young adulthood, there are a subset of EoE children who are now relatively asymptomatic as young adults. Furthermore, in

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our clinical practice most patients diagnosed as adults do not recall symptoms during childhood. This has prompted the question as to whether EoE is a progressive condition from childhood to adulthood, or if pediatric and adult EoE are in fact two separate disease entities.^{8,9} It has been suggested that multiple EoE phenotypes may exist, and that in a subset of patients, pediatric and adult phenotypes may not only have different presenting symptoms, but also a different clinical course.⁶

The primary aim of this study was to determine the clinical outcome of patients who were diagnosed with EoE as children, and who now are young adults. The secondary aims were to determine the prognostic indicators for a favorable outcome in children with EoE as young adults and to evaluate the continued need for medical utilization and maintenance medications.

METHODS

Subject enrollment criteria

Study subjects were recruited from our prospective registry of children with EoE. Children suspected of having EoE underwent biopsies of the mid and distal esophagus and all biopsy specimens were reviewed by expert pediatric gastrointestinal pathologists. Patients with clinical and endoscopic findings consistent with EoE, along with the presence of a minimum of 15 eosinophils per high power field (HPF) in the mid or distal esophagus on biopsy specimens were enrolled in the registry. Demographics, presenting symptoms, biopsy results, and endoscopic findings were collected. Only the index endoscopy that established a diagnosis of EoE was utilized in this study. The presence of concomitant gastroesophageal reflux disease (GERD) was not exclusion for the registry as long as the patient had clinical, endoscopic, and biopsy features consistent with EoE.

Eligible patients for our study included all children with EoE from the pediatric registry whom were now ≥ 18 years of age. Subjects were excluded if they had concomitant gastrointestinal malignancy, celiac disease, or inflammatory bowel disease.

Study protocol

We prospectively hypothesized five baseline characteristics in childhood that may predict continued symptoms as a young adult. These characteristics were (i) gender; (ii) >30 eosinophils per HPF on index esophageal biopsy specimens; (iii) EoE diagnosed under age 12 years; (iv) presence of fibrosis on index biopsy specimens; and (v) presenting symptoms (dysphagia, abdominal pain, heartburn, and vomiting). We subjectively chose a threshold of >30 eosinophils per HPF to assess the possibility that those patients who had a higher eosinophil burden on biopsy were more likely to have an unfavorable outcome despite the accepted

15 eosinophils per HPF for diagnosis. A breakpoint of 12 years of age was chosen to evaluate if patients diagnosed at a younger age (as preteen) were more likely to have a favorable or unfavorable outcome.

Two telephone interview surveys were conducted in this study. The first survey focused on subject's clinical presentation. We obtained data on subjects' current symptoms, medical utilization, medication usage, and food allergies. Subjects were asked to classify their overall outcome of their EoE symptoms into one of the following four categories: resolved, better, same, or worse. A favorable outcome was defined prospectively if a subject reported his or her symptoms were resolved or better. An unfavorable outcome was defined if a subject reported his or her symptoms were the same or worse.

Subjects were also asked about the frequency of the following six symptoms over the past 3 months: nausea/vomiting, abdominal pain, problems swallowing liquids, problems swallowing solids, heartburn, and reflux/acid regurgitation. These symptoms were chosen because they encompass the spectrum of the majority of pediatric and adult EoE symptoms.^{8,9} A time period of 3 months was chosen to minimize subjects' symptom recall bias. Heartburn was defined as a burning pain or discomfort behind the breast bone, and reflux/acid regurgitation was defined as a bitter or sour-taste coming from the stomach into the mouth or throat. Subjects were labeled as asymptomatic if they reported symptoms as none or less than once per month.

The following data on medical utilization over the preceding 12 months was obtained: frequency of clinic visits for EoE, upper endoscopies, food impactions, and emergency room visits. Positive responses were followed by asking the frequency of those occurrences. Patients were also asked if they have taken any steroids (systemic or swallowed topical steroids) or proton pump inhibitors (PPIs) over both the last 30 days and 12 months. In addition, with a detailed food and environmental allergies history was taken. Positive responses were followed by asking if any of their previously diagnosed allergies had resolved.

The second survey that was administered over the telephone was the Mayo Dysphagia Questionnaire (MDQ-30). The MDQ-30 is a validated 28-item instrument to evaluate the severity, frequency, and duration of dysphagia over a 30-day period.^{10,11} It incorporates (i) food avoidance and alteration techniques; (ii) duration of an average meal; (iii) episodes of food impaction, reflux, and heartburn; (iv) history of food and environmental allergens; (v) history of asthma; and (vi) use of medications for heartburn or reflux. Subject's responses allowed the calculation of a dysphagia score (0–100). Scores ≥ 40 are positive for dysphagia. Scores 15–40 are indeterminate, and scores ≤ 15 are negative for dysphagia. MDQ-30 scores were

Table 1 Characteristics of subjects who were diagnosed with EoE, taken from the pediatric registry

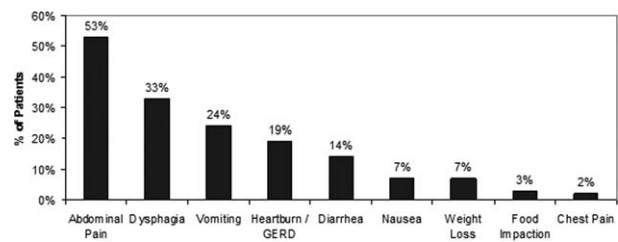
Number of patients	<i>N</i> = 58
Male	37 (64%)
Mean age at EoE diagnosis	12 (4–17)
Endoscopic findings at time of diagnosis	
Vertical lines/Furrows	43 (74%)
Thickened mucosa/Edema	24 (41%)
White specks/Plaques	15 (26%)
Normal	5 (9%)
Erythema	3 (5%)
Decreased vascular pattern	3 (5%)
Rings	2 (3%)
Erosions	1 (2%)
Mean number of eosinophils per high power field at time of diagnosis	
Middle esophagus	37 (2–200)
Distal esophagus	38 (2–200)

compared between subjects with favorable and unfavorable outcomes.

Attempts were made to contact all subjects who met the study criteria using the last known contact information from the pediatric EoE registry. All phone interviews were conducted by two researchers (JWJ, MB). If the researcher was initially unable to contact the subject, up to five reattempts were made. Phone calls were made during the daytime, early evening hours, and on weekends in an effort to capture as many patients as possible. We also left voicemail messages with our contact information when able. All telephone calls were made within a 2-month period. Once contact was made, verbal consent was obtained to administer two questionnaires over the telephone. Once we obtained verbal consent and administered the questionnaires, we extracted the patient's presenting symptoms, endoscopic findings, and biopsy results from the registry. This study was approved by the Indiana University Institutional Review Board.

Data analysis

The primary endpoint of this study was the percentage of EoE patients who reported favorable and unfavorable outcomes as young adults. The secondary endpoints were: (i) the percentage of patients who remained on maintenance steroids or PPIs during the previous 30 days and 12 months; (ii) the percentage of patients who visited a physician, underwent an upper endoscopy, underwent esophageal dilation, or visited an emergency room during the previous 12 months; and (iii) the prognostic indicators for a favorable outcome as young adults. Mantel-Haenszel odds ratio and unpaired *t*-test were used in our statistical analysis. Univariate analysis was used to compare the parameters between subjects with favorable and unfavorable outcome.

**Fig. 1** Presenting symptoms of children who were diagnosed with EoE, taken from the pediatric registry (*N* = 58).

RESULTS

A total of 218 subjects from the pediatric EoE registry met the study entry criteria. Of these 218 subjects, 62 subjects were successfully contacted. Two subjects declined to participate and two subjects were unable to provide consent. Fifty-eight subjects (mean age 21 years old, range 18–28 years old) consented to participate and completed the study. Of the 156 patients who were unable to be contacted by the researchers, the most common reasons were incorrect contact information, failure to answer phone calls, and failure to respond to our voicemail messages.

Clinical characteristics and presenting symptoms as children with EoE

Baseline pediatric clinical characteristics of the 58 subjects are shown in Table 1. Two-thirds of subjects were male, and the mean age at the time of diagnosis was 12 years old. As children, the three most common presenting symptoms were abdominal pain, dysphagia, and vomiting, in 53%, 33%, and 24%, respectively (Fig. 1). The most common findings at the index endoscopy were vertical lines and longitudinal furrows in 74% of patients and edematous mucosa in 41% of patients.

Current symptoms and healthcare utilization as young adults

The mean duration of follow-up between the time of diagnosis and the time of the subject interview was 8.3 years (range 2–16 years). Subjects' assessment of their overall EoE symptom outcome is shown in Figure 2. Nearly half of the subjects reported their symptoms has resolved. Forty-seven subjects (81%) reported a favorable outcome, defined by overall symptoms resolved or improved. The total MDQ-30 scores (mean $\pm$ S.D.) were significantly lower in subjects with favorable outcome (4.6 ± 9.3) compared to those with unfavorable outcome (14.1 ± 17.0), $P = 0.015$.

The prevalence of EoE symptoms as young adults is presented in Figure 3. The majority of subjects had symptoms <1 day per month with respect to abdominal pain, nausea/vomiting, heartburn, regurgitation, dysphagia to liquids, and dysphagia to solids. Six

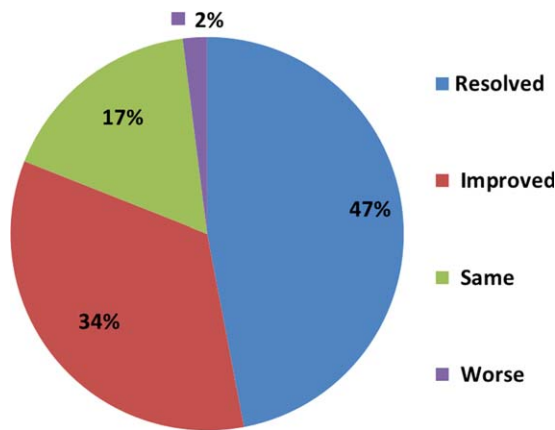


Fig. 2 Patient self-assessment of persistent symptoms as young adults. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

subjects (10%) reported dysphagia to solids >2 days per week. Female subjects were more likely to report the presence of nausea/vomiting as young adults (OR 3.23, CI 0.97–10.6), compared to male subjects. There were no gender differences in other symptoms.

Healthcare utilization and medication use for EoE are shown in Figures 4 and 5. Ten of fifty eight subjects (17%) saw a healthcare professional for EoE in the past 12 months (Fig. 4). Two subjects (3%) had visited an emergency room for symptoms related to EoE, but none underwent esophageal dilation or experienced a food impaction. Thirty-nine percent of young adult subjects reported resolution of one or more of their food allergies diagnosed during childhood. Only a minority of subjects were still taking steroids or PPIs (Fig. 5). The use of PPIs was more common than the use of steroids. In the 27 subjects who reported overall EoE symptom resolution, only one subject (4%) used steroids and two subjects (7%) subjects used PPIs within the previous 12 months.

Predictors of clinical outcome

Potential childhood predictors of clinical outcome as young adults are provided in Table 2. Male patients

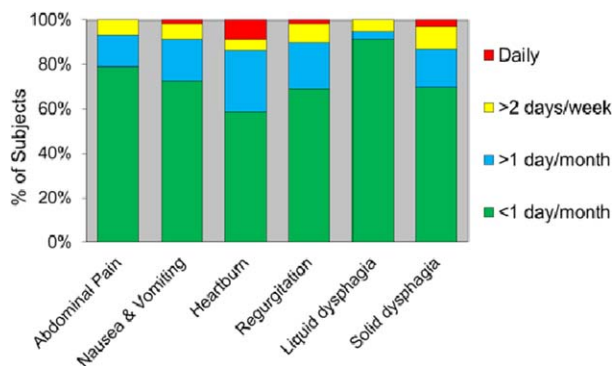


Fig. 3 Residual symptoms of EoE patients as young adults, within the previous 3 months. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

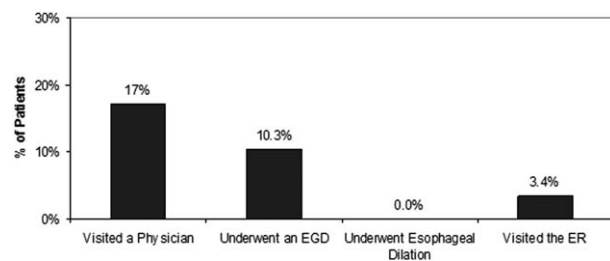


Fig. 4 Healthcare utilization of EoE patients as young adults, within the previous 12 months.

who were diagnosed with EoE as children had a statistically significant favorable outcome compared with female patients (OR 4.13, CI 1.03–16.37).

The presence of fibrosis on the index endoscopic esophageal biopsies was not a predictor of an unfavorable outcome. The presence of dysphagia at the time of diagnosis as children was not a predictor of outcome as young adults. However, of all presenting symptoms, dysphagia was the most likely symptom to persist as young adults (OR 6.29, CI 1.85–21.38).

DISCUSSION

This study describes the clinical outcome of patients who were diagnosed with EoE as children and who are now young adults. Our results reveal that 81% of these children reported resolution or improvement of their symptoms as young adults. Of the five preselected baseline characteristics at the time of diagnosis, gender was the only significant predictor of outcome. Male children with EoE had a more favorable outcome than female children. Diagnosis at a younger age (<12 years), greater concentration of mucosal eosinophils (>30 eosinophils per HPF), presence of mucosal fibrosis, and presenting symptoms did not predict outcome as young adults. Dysphagia was the most likely symptom to persist into young adulthood suggesting fibrosis and esophageal remodeling occurred as a result from chronic inflammation. We can speculate that the early dysphagia may have resulted from an inflammatory response and esophageal dysmotility early in the disease course. This particular phenotype as a child may predict who will experience the remodeling

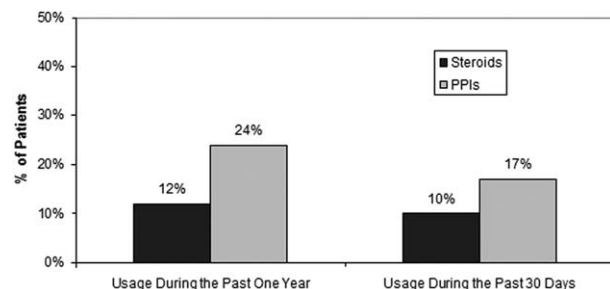


Fig. 5 Medication utilization of EoE patients as young adults, within the previous 12 months and 30 days.

Table 2 Predictors of outcome in pediatric EoE patients as young adults

	Odds ratio	95th Confidence interval
Male	4.13	1.03–16.37
#Eosinophils >30 per HPF	1.91	0.49–7.42
EoE diagnosis <12 years age	0.97	0.26–3.62
Fibrosis on biopsy	0.67	0.1–2.51
Presenting symptoms:		
Dysphagia	1.38	0.32–5.91
Abdominal pain	0.59	0.15–2.31
Heartburn	0.55	0.19–2.52
Vomiting	0.47	0.12–1.94

cascade as young adults and develop a narrowed esophagus with fibrotic rings. Presenting with a different clinical (nausea, vomiting, abdominal pain, or FTT) phenotype in childhood may have a favorable outcome in adulthood as the predominant presentation in adults is dysphagia and food impaction.

Previous studies suggested that EoE is a chronic condition within their respective pediatric and adult populations.^{6,12,13} However, the transition period of EoE from childhood to young adulthood is still unclear. In a retrospective review by DeBrosse *et al.*, children with esophageal eosinophilia had persistent symptoms 15 years after their initial presentation.¹⁴ Study groups were based only by histologic features with ≥ 15 eosinophils/HPF identified as EoE and < 15 eosinophils/HPF identified as chronic esophagitis. No clinical assessments or endoscopic features were used for initial diagnosis. Forty percent of the children had food impaction, 14% required dilation for esophageal stricture, and 41% reported ongoing care by a gastroenterologist. However, they reported that the majority of their patients did not receive adequate treatment for EoE following their initial presentation and that only 27% of the pediatric patients with esophageal eosinophilia ultimately received a diagnosis of EoE which was self-reported. In our study, the diagnosis of EoE was made based on the composite data from clinical, endoscopic, and histologic findings from our prospective pediatric EoE registry which is consistent with today's standard practice.

To date, only one other study has described the transition of EoE from children into young adulthood. Menard-Katcher *et al.* described 53 young adult patients (mean age 20.5 years) who were diagnosed EoE at a mean age of 13.5 years old.¹⁵ In their study, 50% of their patients took PPIs within the last 30 days as an adult, compared to only 17% of our patients. A similar percentage of patients in their study (6%) were taking swallowed topical steroids, compared with our study (10%). Interestingly, patients in both studies had very low MDQ-30 scores during follow-up. In our study, patients with both favorable and unfavorable outcomes had mean scores which were below the threshold typical for patients with dysphagia. This

could suggest poor sensitivity of the MDQ to capture ongoing symptoms of EoE in adults. It is likely that the MDQ-30 may not adequately reflect dysphagia due to conditions other than esophageal strictures, for which the MDQ-30 is validated. This reinforces the importance of the continued validation of EoE quality-of-life questionnaires and underscores the need for patient reported outcomes research.^{16,17}

This study has some limitations. While this study does prospectively evaluate the progression of disease across age groups, the number of patients is relatively small with respect to evaluating long-term outcomes. It is not a true longitudinal prospective cohort study, but rather a follow-up study to evaluate young adults who were diagnosed with EoE as children. This is a single-center study from a large, tertiary-care referral center and as a result, it is not clear if these outcomes mirror those seen in community-based practice. A large portion of the data collected was subjective and the use of these questionnaires required patients to recall data from the past year. This therefore introduced the potential for recall bias. The mean duration of follow-up was relatively short at 8.3 years and given that the average patient age in this study is 20.9 years old, it is not known if these outcomes can also be attributed to older adults. We also did not repeat an EGD to correlate patient outcomes in this study with objective endoscopic and histologic data.

Of the 218 patients who met our inclusion criteria, our patient contact rate was low (62/218, 28%) but, this was similar to the DeBrosse *et al.* study in which 30% of all patients in the retrospectively identified EoE group, for which they had contact information ultimately completed their study questionnaires. Our rate was slightly lower than the study by Menard-Katcher *et al.* (37%). Our rate was low in large part due to inaccurate current contact information as patients and their families had either moved or changed telephone numbers. In addition, per family members, many patients were away at college, and it simply proved difficult to establish telephone contact with this age group.

Our patients did not all undergo formal pH testing at the time of diagnosis to formally evaluate for GERD as the cause of their esophageal eosinophilia. In addition, there was not a protocol which placed all patients on an 8-week course of a PPI following diagnosis to exclude PPI-responsive esophageal eosinophilia (PPI-REE) as this disease entity was not well-established at the time of registry creation. While we cannot rule-out GERD and PPI-REE as confounding factors, we believe that our patient group does reflect true EoE given the conglomerate of symptoms and endoscopic findings, specifically longitudinal furrows. The three most common endoscopic findings at the time of diagnosis were furrows (74%), thickened mucosa/edema (41%), and white specks (26%). Dellon *et al.* previously reported that linear furrows and white

plaques independently predicted EoE compared with GERD, and that inflammatory-type findings were more commonly visualized in pediatric patients with EoE.¹⁸

In summary, this study reveals that the majority of patients diagnosed with EoE as children had resolution or improvement in symptoms as young adults. This suggests that EoE may in fact be two different disease entities in children and adults or this reflects different phenotypes of the same disease. Supporting the phenotypic diversity is the persistence of dysphagia from childhood to adulthood in some patients linking this as a potential predictor of lifelong illness from EoE. Given the paucity of data on the progression of EoE across age groups, further studies are needed which include larger cohorts of patients followed longer into adulthood.

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