

The Role of the Otolaryngologist in the Evaluation and Diagnosis of Eosinophilic Esophagitis

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Objective: To describe the clinical presentation and role of the otolaryngologist in the evaluation of eosinophilic esophagitis (EoE) at a tertiary pediatric hospital.

Study Design: Retrospective review.

Methods: Records from pediatric patients with a diagnosis of EoE from 2003 to 2015 were reviewed. Study variables were analyzed to compare patients presenting to different specialties.

Results: Two hundred and fifty-one patients with EoE were evaluated. The median age at diagnosis was 9.0 years (range 0.8–19.0); 73% were male. Sixty-seven percent of patients initially presented to gastroenterology and 18% to otolaryngology. Time from initial presentation to diagnosis did not differ between the patients presenting to the two specialties (median 2.3 vs. 2.0 months, $P = 0.510$). Overall, 26% presented with airway symptoms (stridor, chronic cough, croup, or dysphonia). Patients diagnosed by the otolaryngology service were younger (3.4 vs. 10.4 years, $P < 0.0001$), had a higher incidence of airway symptoms (68% vs. 15%, $P < 0.001$), and demonstrated fewer gastrointestinal symptoms (86% vs. 100%, $P < 0.001$).

Conclusion: Patients with EoE frequently present to otolaryngology undiagnosed in the first 5 years of life, making esophagoscopy with biopsy an important adjunct to airway endoscopy in children with refractory aerodigestive symptoms. Otolaryngologists are uniquely poised to facilitate early diagnosis and initiation of therapy for these children, potentially reducing long-term sequelae.

Key Words: Eosinophilic esophagitis, atopy, dysphagia, airway, esophagoscopy.

Level of Evidence: 4.

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INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic, immune-driven inflammatory condition of the esophageal mucosa. Diagnosis requires symptoms of esophageal dysfunction, esophageal eosinophilia on esophageal biopsy, and exclusion of alternative causes of esophageal eosinophilia.^{1,2} Recently, there has been increased recognition for this clinical entity as a cause of gastrointestinal morbidity and reduced quality of life in affected children.³ Attwood initially described EoE in 1993 after studying a subset of children with esophageal dysfunction, negative pH probe testing, and esophageal eosinophilia.⁴ Since its description, epidemiological studies seem to indicate a rising incidence in the United States.⁵

Over the last 20 years, clinical studies have better defined the epidemiology, presentation, treatment,

natural history, and long-term complications associated with this disease. Not surprisingly, EoE is characterized by a high incidence of comorbid atopic disorders such as allergic rhinitis, asthma, and eczema.⁶ Although inflammatory in its early stages, EoE can progress to a fibrostenotic phase characterized by esophageal stricture and chronic dysphagia.¹

Eosinophilic esophagitis is a chronic disease that traditionally was exclusively managed by providers in gastroenterology and allergy/immunology. Recent studies, however, have brought attention to airway manifestations of this disease and implicated EoE as a possible cause of recurrent croup, stridor, dysphonia, and chronic cough in some children.^{7–10} In a study by Hill et al., 3.7% of patients who were offered diagnostic endoscopy for refractory airway symptoms had EoE on esophageal biopsy.¹¹ Two retrospective series of patients with recurrent croup found the cause to be EoE in 6.2% and 10.2% of cases, respectively.^{8,9} Histologic evidence supplements this growing clinical evidence of airway manifestations of EoE. For example, Yawn et al. found laryngeal mucosal eosinophilia in 33% of children with known EoE.¹²

As a consequence, the role of the otolaryngologist in the diagnosis and management of these children is evolving. Although most of the longitudinal care remains in the realm of the gastroenterologist, in up to 15% of cases these children first may present to an otolaryngologist.¹³ In addition to airway symptomatology, these children have elevated rates of comorbid otolaryngologic

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diagnoses such as recurrent otitis media, chronic sinonasal disease, and adenotonsillar disease.¹⁰

Given that this remains a relatively new clinical entity, there currently is little published on the multidisciplinary diagnosis and management of this disorder in the pediatric academic setting. The intention of this study is to describe the clinical experience of a large pediatric tertiary referral center with EoE, document treatment, and referral patterns, and specifically investigate the role of the otolaryngologist.

MATERIALS AND METHODS

After study approval by the University of Pittsburgh Institutional Review Board, the electronic medical records of patients with a diagnosis of eosinophilic esophagitis based on International Classification of Diseases, Ninth Revision, coding were reviewed. Patients 21 years of age and younger were included if they were diagnosed with EoE at the Children's Hospital of Pittsburgh (Pittsburgh, PA) between 2003 and 2015. Diagnostic criteria for EoE included symptoms of esophageal dysfunction, esophageal eosinophilia with >15 eosinophils/high-powered field (HPF) in esophageal biopsy specimens, and exclusion of competing causes of esophageal eosinophilia. We included only patients who underwent diagnostic esophagoscopy with biopsy at our institution. All esophageal biopsies were reviewed by our pathology department and underwent routine processing with hematoxylin and eosin staining. The diagnostic threshold of 15 eosinophils/HPF was used based on literature review and a recent national consensus statement.² Patients were excluded if they had histologic or clinical resolution with proton pump inhibitor (PPI) therapy consistent with PPI-responsive esophageal eosinophilia. As such, all patients in this study underwent two esophagoscopies to confirm the diagnosis of EoE and to exclude PPI-responsive esophageal eosinophilia.

Data was collected through independent review of the electronic medical records. Basic information extracted from the records included patient demographics, date of presentation, clinical department to which they initially presented, medical history, latency from presentation to diagnosis, and clinical course. Age at diagnosis and presenting symptoms were reviewed. We specifically split presenting symptomatology into two groups: airway symptoms and gastrointestinal (GI) symptoms. Gastrointestinal symptoms included dysphagia, abdominal pain, and chronic nausea or emesis. Airway symptoms were defined as chronic cough, stridor, recurrent croup, and dysphonia.

When the diagnostic endoscopy was undertaken by the otolaryngology service, this evaluation included flexible fiberoptic laryngoscopy, direct laryngoscopy, rigid bronchoscopy, and rigid esophagoscopy with biopsy. Two sets of esophageal biopsies were taken, one from the proximal esophagus and one from the distal esophagus. If results of the biopsy were consistent with EoE, patients were placed on oral PPI therapy and referred to gastroenterology for follow-up esophagoscopy and biopsy in 3 months.

We specifically reviewed atopic comorbidities such as allergic rhinitis, asthma, and eczema. Any additional diagnoses established during otolaryngology consultation were recorded. Pathologic and clinical results of esophagoscopy and any diagnostic airway endoscopy were noted. Results of any food allergy testing were also reviewed. The patient's treatment course was studied, including medical therapy with acid suppression, topical steroid therapy, dietary changes, and any additional surgical interventions such as balloon dilation or foreign body removal.

TABLE I.
Patients with Eosinophilic Esophagitis at the Children's Hospital of Pittsburgh (Pittsburgh, Pennsylvania).

Patient Variables	Total Patients (n = 251)	
	Number	%
Age (years), Median	8	0.8–19
Follow-up (months), Median	17	1–97
Gender (male)	183	73%
Family history of EoE	9	4%
Presenting location		
Otolaryngology	44	18%
Gastroenterology	169	67%
Allergy/immunology	7	3%
Emergency Department	31	13%
Ethnicity		
Caucasian	228	91%
African American	16	6%
Atopic Disorders		
Allergic rhinitis	117	47%
Eczema	58	23%
Asthma	87	35%

EoE = eosinophilic esophagitis.

We also reviewed any emergency department visits or hospital admissions related to their EoE.

Descriptive statistics of all study variables were generated with the assistance of commercial statistical software (Stata SE/13, StataCorp LP, College Station, TX). Mann-Whitney U, Fisher exact, and chi-squared tests were used to compare patients presenting to different specialties. All statistical tests were two-sided, and *P* values were evaluated such that consideration for statistical significance was *P* < 0.05.

RESULTS

The medical records of 305 patients were reviewed for inclusion, of which 251 met criteria for further study. Patient characteristics and demographics can be found in Table I. The median age at diagnosis was 9.0 years, and 73% (183 of 251) were male. Of our cohort, 91% were Caucasian. A family history of EoE was present in 4% of patients. With respect to atopic comorbidities, the incidence of asthma, eczema, and allergic rhinitis in this group was 35%, 23%, and 47%, respectively. Results of in vitro or skin allergy testing were available for 61% (153 of 251) of patients, and 69% (1,050 of 153) had sensitivities to food antigens.

The departmental sites of initial patient presentation were as follows: gastroenterology 67% (169 of 251), otolaryngology (ENT) 18% (44 of 251), allergy/immunology 3% (7 of 251), and emergency department (ED) 13% (31 of 251). Patients seen in the ED were often discharged with scheduled follow-up with GI. Of those patients evaluated initially by ENT, 82% (36 of 44) were diagnosed with esophageal eosinophilia during diagnostic panendoscopy. These patients were placed on PPI therapy and referred to GI for definitive management.

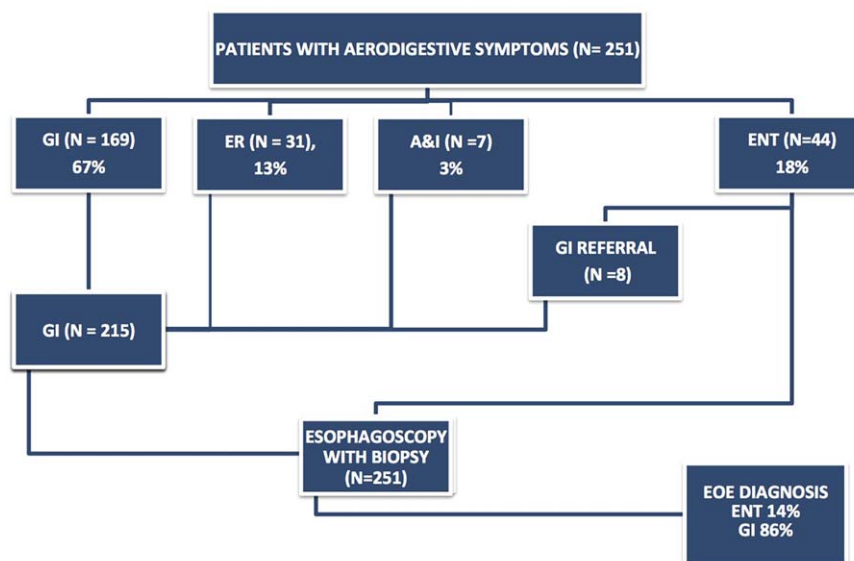


Fig. 1. Diagnosis and referral patterns for patients with eosinophilic esophagitis (EoE) presenting to Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania. A&I = allergy and immunology; ENT = ear, nose, and throat; EOA = eosinophilic esophagitis; ER = emergency room; GI = gastroenterology. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

The patients underwent repeat flexible endoscopy with biopsy to confirm the diagnosis of EoE. Of those patients seen initially by ENT, 18% (8 of 44) were later diagnosed by the GI service. Median time to diagnosis did not depend on the site of initial presentation (2.0 months for ENT vs. 2.3 months for GI, $P = 0.510$). Patients who initially presented to ENT were significantly younger than those presenting to GI (median age 3.4 years vs. 10.4 years, $P < 0.0001$). A visual representation of patient care patterns is found in Figure 1. The percentage of patients diagnosed by the ENT service decreased as age of presentation increased (Fig. 2).

Symptoms on presentation are summarized in Table II. Symptom prevalence is summarized for the entire cohort and then based on the location at which the patient first presented. Overall, 26% (64 of 251) of patients presented initially with airway symptoms including chronic cough, dysphonia, stridor, or recurrent croup. Ninety-seven percent (243 of 251) of patients had GI symptoms on presentation, the most common of which were dysphagia, recurrent emesis/nausea, and abdominal pain, or food regurgitation. In the subset of patients who presented to ENT, airway symptomatology was more common (68% vs. 15%, $P < 0.001$) and GI symptomatology was more rare (86% vs. 100%, $P < 0.001$) compared with those who presented to GI. Only 14% (6 of 44) presenting to ENT did so with isolated airway symptoms in the absence of any GI complaints.

Patients presenting initially to GI presented later in life (as mentioned) and did so with a preponderance of GI symptoms (100%) and less airway symptomatology (15%) relative to those presenting to otolaryngology. All patients seen initially by allergy/immunology or the ER were referred to GI for endoscopy. Eight patients were seen by otolaryngology initially, no endoscopy was recommended, and they subsequently were seen by GI and later diagnosed on endoscopy.

Findings at the time of esophagoscopy can be found in Table III and endoscopic examples in Figure 3. Linear

furrowing was the most common abnormality noted (59%). Endoscopic appearance of the esophagus was noted to be normal in 17% of patients with pathologically confirmed esophageal eosinophilia.

Airway endoscopy including flexible laryngoscopy and rigid bronchoscopy was performed in 25% (63 of 251) of the cohort. Table III demonstrates findings on airway endoscopy. Only 43% (27 of 63) of these patients' airway endoscopy was without any structural abnormality. Common findings included tracheal cobblestoning (30%, 19 of 63), laryngomalacia (14%, 9 of 63), and subglottic stenosis (SGS) (13%, 8 of 63). All patients with SGS had grade I or grade II stenosis; five of eight (63%) resolved on future endoscopies.

Medical management was provided by the GI service at our hospital. Eighty-six percent of patients were treated with an oral PPI. Possible trigger foods were eliminated from the diets of 43% (110 of 249) of patients. Topical steroids were used in 58% (144 of 249) of patients. Three patients (1%) required endoscopic balloon dilation for esophageal strictures, and four patients (2%) required intervention for food impaction. The

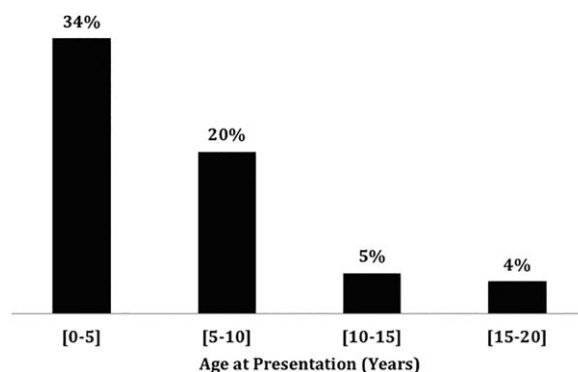


Fig. 2. Percentage of patients with eosinophilic esophagitis diagnosed by the otolaryngology service based on age of presentation to Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania.

TABLE II.
Presenting Age, Latency to Diagnosis, and Symptoms of Eosinophilic Esophagitis Based on Site of Initial Presentation.

	All Patients (N = 251)		Otolaryngology Clinic (N = 44)		Gastroenterology Clinic (N = 169)		P Value*
	Mean	Range	Mean	Range	Mean	Range	
Age (years), range	9	0.8–19.0	3.4	0.9–16.8	10.4	0.8–19.0	0.01
Time to diagnosis (months)	2.1	0.0–113.8	2.0	0.0–113.8	2.3	0.0–139.1	0.51
	N	%	N	%	N	%	P Value*
Symptoms (Gastrointestinal)	243	97	38	86	169	100	0.01
Dysphagia	109	43	26	59	60	36	0.01
Abdominal pain	142	57	15	34	105	62	0.01
Nausea/emesis	122	49	17	39	91	54	0.03
Symptoms (Airway)	64	26	30	68	25	15	0.01
Chronic cough	50	20	18	41	25	15	0.01
Croup	11	4	6	14	2	1	0.01
Stridor	10	4	6	14	6	4	0.01
Dysphonia	17	7	9	20	6	4	0.01

*This P value reflects the comparison of the cohort presenting to otolaryngology versus the cohort presenting to gastroenterology.

incidence of other otolaryngologic diagnoses and surgeries in this cohort was high and can be found in Figure 4.

Figure 1 depicts the treatment and referral patterns for eosinophilic esophagitis seen in our study. Of note, eight patients were seen by otolaryngology and subsequently diagnosed by GI at a later time. In 87.5% (7 of 8) of cases, the patients presented to the otolaryngology clinic with isolated GI symptoms (dysphagia, recurrent emesis) and were not offered diagnostic endoscopy. They were treated empirically for GERD and then all were referred to GI by our service for refractory symptomatology. One patient was seen in our clinic with predominately airway symptoms (cough, intermittent stridor) and underwent airway endoscopy without esophagoscopy. It was unclear why esophagoscopy was deferred in this case. The patient was subsequently diagnosed by GI 40 months later.

DISCUSSION

Eosinophilic esophagitis is a chronic disease that, like other atopic disorders in the United States, has been increasing in incidence and is the subject of considerable current investigation.¹⁴ Classically a disease primarily concerning the gastroenterologist, recent research has emphasized several upper aerodigestive manifestations of this disease. Consequently, the role of the otolaryngologist in the diagnosis of this disease is changing.

This study represents one of the largest series of patients with EoE presenting to multiple departments at a tertiary children's hospital. Ultimately, 14% of patients were diagnosed by the otolaryngology service on the basis of esophageal biopsy results during diagnostic panendoscopy, often for refractory upper aerodigestive complaints. In only 18% (8 of 44) of cases evaluated by the otolaryngology service was the diagnosis missed and subsequently made by the GI service.

Our findings suggest that our otolaryngology service is diagnosing EoE frequently and efficiently. Ultimately, 82% (36 of 44) of undiagnosed EoE patients presenting to our clinic were offered diagnostic panendoscopy for their symptomatology. The median latency to diagnosis among patients diagnosed by the otolaryngology service was 2.0 months, similar to that for patients diagnosed by the GI service (2.3 months). This has not been the experience of other large centers. Given the vague symptomatology that often characterizes this disease, the latency to diagnosis described in the literature is approximately 7 years.^{15,16} In a recent large study from the Children's Hospital of Philadelphia, 20% of patients were evaluated by otolaryngology, but the diagnosis was missed in 68% of cases.¹³ They concluded in this article that otolaryngologists need to have a higher level of suspicion of this disease process when evaluating patients with dysphagia. Our data seems to suggest that our level of awareness of this entity is increasing and that evaluating the esophagus at the time of airway examination is beneficial.

TABLE III.
Endoscopy Results in Patients With Eosinophilic Esophagitis.

Esophagoscopy (N = 251)			Airway Endoscopy (N = 63)		
	N	%		N	%
Normal	43	17	Normal	27	43
Mucosal edema	75	30	Laryngomalacia	9	14
Trachealization	3	1	Tracheomalacia	3	5
Linear furrowing	146	59	Laryngeal cleft	4	6
Ulceration	12	5	Tracheal Cobblestoning	19	30
Mucosal exudate	25	10	Subglottic stenosis	8	13

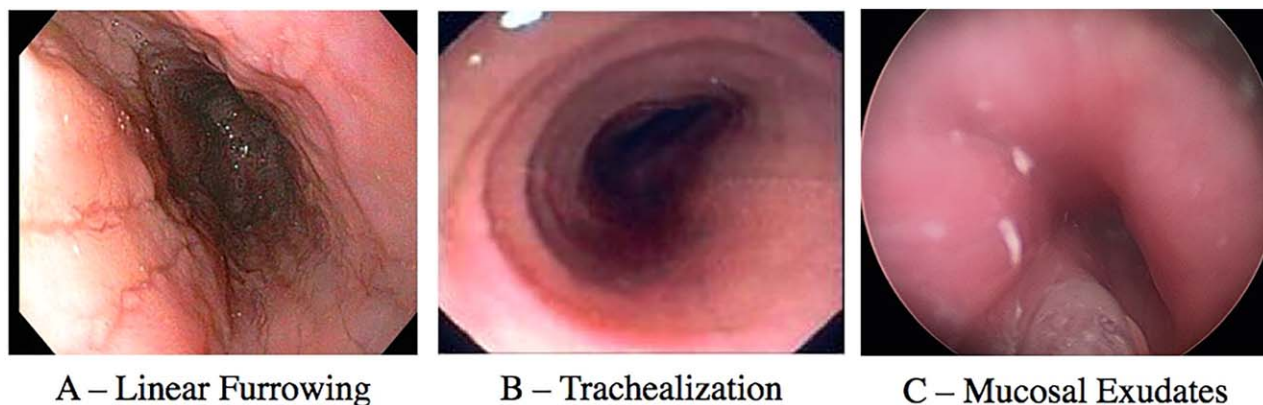


Fig. 3. Common endoscopic abnormalities seen in patients with eosinophilic esophagitis. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

Our study also helps explain why these patients frequently present to an otolaryngology clinic. Previous studies have described extraesophageal manifestations of EoE; however, the incidence of these manifestations and associated airway symptoms in the general EoE population is not quite clear. In the present study, 26% of patients had symptoms of chronic cough, croup, stridor, or dysphonia. Interestingly, patients presenting initially to otolaryngology were unique in that they had a higher incidence of airway symptomatology and a lower incidence of GI complaints. In fact, 14% of patients presenting to otolaryngology had no GI symptoms. This has not previously been described.

In our experience, patients diagnosed by otolaryngology were significantly younger than those diagnosed by the GI service (median age 3.4 vs. 10.4 years). In the otolaryngology literature, the mean age at diagnosis has been reported to range from 4.5 to 4.7 years.^{7,11,12} In the corresponding GI literature, mean age at diagnosis has ranged from 6.2 to 10.5 years. In our study, 34% (28 of 82) of patients aged < 5 years presented to otolaryngology compared with 4% (2 of 50) of patients aged 15 to 19 years. Ultimately, the significance of these differences is unclear. However, our study suggests that when these patients present to the otolaryngologist, they do so most

often in the first 5 years of age with a combination of upper airway and swallowing dysfunction.

At our center, we have a low threshold to perform diagnostic airway endoscopy and esophagoscopy with biopsy in patients with refractory aerodigestive symptomatology. Although no surgical procedure is without risk, rigid esophagoscopy generally is felt to be a very safe procedure. A previous study from our institution examined records from 2,429 patients undergoing rigid diagnostic esophagoscopy, and no complications were reported.⁷ It is important to note that 17% of patients in our study had grossly normal esophageal mucosa during endoscopic exam, which highlights the need for esophageal biopsy even in the setting of normal esophageal appearance.

The fact that our otolaryngology division seems to be diagnosing this condition early leads one to question whether this alters the disease course. In the literature, there are no studies suggesting that early diagnosis and early implementation of therapy leads to improved long-term outcomes. However, one might surmise that, given the chronic fibroinflammatory nature of EoE, early identification and institution of medical therapy may prevent future morbidity.

In addition to airway symptomatology driving referrals, these patients often have comorbid otolaryngologic diagnoses that prompt evaluation in an ENT clinic. One study by Kelly et al. found that 33% of EoE patients undergo surgery by an otolaryngologist most commonly for chronic otitis media, sleep-disordered breathing, adenotonsillar disease, and chronic rhinosinusitis.¹⁰ We saw similarly high rates of ENT surgery performed in our patient cohort.

Ultimately, airway endoscopy was performed in 25% of patients, frequently revealing abnormalities. Perhaps the most important finding was that 13% of patients had grade I or II SGS, and four of eight (50%) instances occurred in the absence of any previous intubation history. Most (5 of 8) patients had resolution of their SGS on follow-up airway endoscopy after institution of medical management of their EoE. The association of EoE with idiopathic or inflammatory SGS has been previously described. Interestingly, a small study by Hartnick et al. found that untreated EoE was

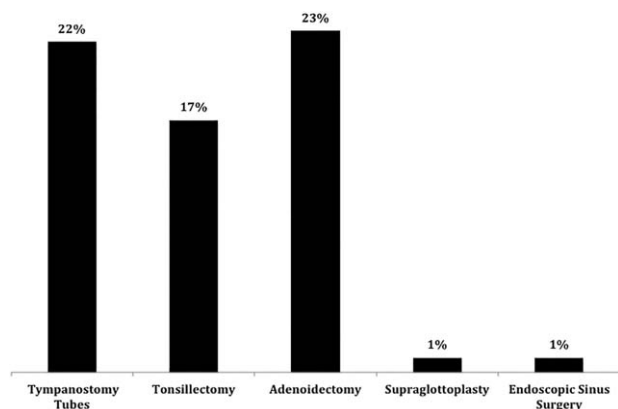


Fig. 4. Ear, nose, and throat surgeries in patients with eosinophilic esophagitis.

associated with poor outcomes following laryngotracheal reconstruction.¹⁷ Although this needs to be studied further, we feel that esophagoscopy and biopsy is an important component in the workup of any patient with subglottic stenosis, especially those with no intubation history.

CONCLUSION

In conclusion, patients with EoE frequently present to otolaryngologists in early childhood with refractory aerodigestive symptomatology or comorbid otolaryngologic diseases. Given that these patients often present undiagnosed, we must have a high level of suspicion for this diagnosis and a low threshold to perform esophagoscopy with biopsy for investigation. These patients often present to otolaryngology in the first 5 years of life. Therefore, the otolaryngologist is uniquely poised to facilitate early diagnosis, prompt referral to GI, and early institution of medical therapy for EoE, potentially leading to reduced long-term sequelae.

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