HSPI The Open Access Publisher

JAPCH JOURNAL OF ADVANCED PEDIATRICS AND CHILD HEALTH
ISSN 2689-9817

Research Article

Risk factors for esophageal strictures in children and adolescents with eosinophilic esophagitis

Vijayalakshmi Kory[1]*, Thirumazhisai S Gunasekaran[2], Kumail Hussain[3], Tiffany Patton[4], Yi Li[5], Cheryl LeFaiver[5] and James Berman[2]

[1]Advocate Children's Hospital, 1775 Dempster Street, Park Ridge, IL 60068, USA

[2]Advocate Children's Hospital, Loyola Medical Center, and University of Illinois, 1775 Dempster Street, Park Ridge, IL 60068, USA

[3]MD Candidate, Rosalind Franklin University of Medicine and Science, North Chicago, IL 60064, USA

[4]University of Chicago, Comer Children's Hospital, 5839 S. Maryland Ave, Chicago, IL 60637, USA

[5]Advocate Center for Pediatric Research, Advocate Aurora Research Institute, 4440 West 95th Street, Oak Lawn, IL 60453, USA

More Information

***Address for Correspondence:** Thirumazhisai S Gunasekaran, Advocate Children's Hospital, Loyola Medical Center, and University of Illinois, 1775 Dempster Street, Park Ridge, IL 60068, USA, Email: ts.gunasekaran@aah.org

Submitted: October 18, 2022
Approved: October 26, 2022
Published: October 27, 2022

How to cite this article: Vijayalakshmi K, Gunasekaran TS, Hussain K, Patton T, Li Y, et al. Risk factors for esophageal strictures in children and adolescents with eosinophilic esophagitis. J Adv Pediatr Child Health. 2022; 5: 033-038.

DOI: 10.29328/journal.japch.1001050

Keywords: Eosinophilic esophagitis; Risk factors; Dysphagia; Strictures; Food impaction

Abstract

Studies in children with eosinophilic esophagitis (EoE) have reported esophageal strictures but none have examined risk factors associated with strictures.

Aim: To assess risk factors associated with strictures in children with EoE.

Methods: In this retrospective study, children with EoE seen over 20 years were separated into two groups; with and without strictures. Physical features, CBC, endoscopic findings, and biopsy of the distal and mid-esophagus were captured. Statistical significance with *p* - value and multivariate logistic regression was done.

Results: Total patients 222 and 20 (9.1%) had strictures. Mean age of stricture patients 12.7 years (range 7-18) and non-stricture 9.3 years (range 1-17) ($p = 0.006$). Among stricture patients following were prevalent and significant; dysphagia (stricture 100% *vs.* non-stricture 41.6%, $p = 0.0005$) and food impaction (70.04% *vs*. 4%, $p = 0.0005$); EGD: rings and exudates were strongly associated with stricture, 45.0% *vs.* 4.5%, $p = 0.0005$ and 60% *vs.* 30.7%, $p = 0.008$, respectively. Abdominal pain was lower in the stricture group (5% *vs.* 31.2%, $p = 0.017$). Eosinophil counts were numerically more in the stricture group but not significant. Multivariate logistic regression confirmed that strictures are likely to occur among patients with dysphagia ($p = 0.02$, OR = 11.7, 95% LCL 2.0) and food impaction ($p = 0.0001$, OR = 80.9, 95% LCL 15.4), respectively, adjusted for age and gender.

Conclusion: EoE children with dysphagia or food impaction have a higher chance of having an esophageal stricture. These EoE children 12 years or over with exudates or rings on endoscopy, should be treated and carefully monitored, to reduce the risk of stricture formation.

Introduction

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated disease, associated with eosinophilic inflammation of the esophagus [1-3]. Since its description more than 30 years ago, the worldwide incidence and prevalence of EoE have increased rapidly, and is considered a common disease in developed countries [4]. The prevalence according to prior studies in adults ranges from 78 to 111 per 100,000 people [5]. In children the incidence of EoE varies from 0.7 to 10/100,000 per person-year and the prevalence ranges from 0.2 to 43/100,000 [6]. With antigen insult to the esophagus, eosinophilic inflammation begins in the peripapillary area within the deep mucosal layers of the esophagus and then progresses to the superficial layers. Basal zone hyperplasia and lengthening of lamina propria papillae are secondary changes to the antigen insult and increase with the duration of the insult [7]. Degranulation of eosinophils with cytotoxic and cytokine release is another mechanism of inflammation. This results in the desquamation or degeneration of cells,

mobilization of more eosinophils, and tissue remodeling with consequential fibrosis. Several mediators released from inflammatory cells are involved in driving esophageal remodeling in EoE, with a particular role for transforming growth factor TGF -β1 similar to that observed in airway remodeling associated with bronchial asthma [8-10]. In addition to TGF -β1 signaling, other mechanisms involved in EoE remodeling include epithelium-mesenchymal transition and angiogenesis [11,12]. This ongoing remodeling due to persistent inflammation in EoE may adversely affect esophageal function, leading to dysmotility, esophageal rigidity, and, finally esophageal stricture formation [13].

Recently, three phenotypes of EoE have been described with diverse endoscopic features: inflammatory (white exudates and/or furrows), fibro-stenotic (rings and/or strictures which may be focal or involving a longer segment), and mixed type inflammatory/fibro-stenotic (with combined features) [14,15]. Esophageal strictures in adults are grouped into a short segment, narrow caliber, and extremely narrow caliber esophagus depending on the length of involvement and degree of narrowing [15]. Previous studies in children with EoE, including ours, have described characteristic features and outcomes of the fibrostenotic phenotype of EoE and its subgroups [16-18]. However, none have examined risk factors associated with esophageal strictures in children with EoE.

Aim

The purpose of this study is to compare clinical features, endoscopic findings, histology, and treatment of EoE in pediatric patients with and without esophageal strictures to determine risk factors associated with the development of strictures.

Methods

In this retrospective study, all children and adolescents with EoE seen over a period of 20 years (01/2001 and 04/2021) were included. Diagnosis of EoE was confirmed as follows: esophageal biopsy with 15 or more eosinophils/HPF, no increase in eosinophils in the stomach or duodenum, with a symptom of esophageal dysfunction with a negative esophageal pH study (Bravo, Given Imaging, USA) and pre-endoscopy treatment with proton pump inhibitors (PPI-omeprazole 20 mg - 40 mg or lansoprazole 30 mg – 60 mg/day) or in accordance with recent Guidelines it was not applied. Patients with increased eosinophils in the stomach and duodenum, celiac disease, or Crohn's disease were excluded. Diagnostic criteria were consistent with Consensus Guidelines which varied over the years spanning our study period [1-3]. Patients were divided into two groups: with stricture and without stricture. The stricture was defined as the inability to pass a regular endoscope (Olympus Medical Systems Corporation, Tokyo, Japan; outer diameter- 9 mm and channel size 2.8 mm) or when passed developed a significant mucosal tear and was included for this study. Same-brand endoscopes were used for the study period. Mucosal fragility or crepe paper appearance was not taken as evidence of stricture [14-16]. Stricture prevalence was calculated within the entire study population and within patients presenting with dysphagia.

The following data were collected from the medical records: clinical symptoms, physical findings, associated allergic diseases, complete blood count with differential, and complete metabolic profile [19]. Symptoms were queried to all patients based on esophageal symptoms, with knowledge of variable presentation in children of different age groups and including abdominal pain. The duration of the symptoms was not captured. Endoscopic findings of strictures, furrows, white spots/exudates, concentric rings, and friability were also collected. Histological data were based on three to four biopsies obtained from the descending duodenum, stomach, distal and mid-esophagus. A dysphagia score was assigned for applicable patients: absent-0, mild-1, severe-2 [20] and an additional score for food impaction- 3 [20,21]. Food impaction was defined as impacted food requiring endoscopic removal or a visit to the emergency department [2]. Peak and mean esophageal eosinophil counts at the highest concentration of eosinophils per high power field (400x), from the distal and mid esophagus, were taken at diagnosis [1-3,21]. Reading of the biopsies was done within a group of four pathologists and they were trained by the lead pathologist on the interpretation. Dilation was performed with Savary-Gillard hollow-centered dilators passed over an endoscopically placed guide wire, or with balloon dilation via the endoscope. All dilations were done by one author (TG) and the endoscopy was done by the same author and three others, and all were familiar with the interpretation of EoE endoscopic findings. Prior to planned dilation the treatment was with topical steroids; fluticasone 880 mcg/day for ages 1 - 10 years and 1760 mcg/day for 11 - 18 years, in four divided doses, or budesonide 0.5 mg - 1 mg BID for patients up to 5 feet height and 1 mg - 2 mg BID for those over 5 feet, for six weeks. Institutional Review Board approval was obtained through Advocate Health Care, Oak Brook, Illinois, prior to data collection.

Statistical analysis

Data were summarized using means/standard deviations if normally distributed, medians/interquartile ranges for discrete counts, and frequencies/proportions when categorical. To compare the stricture versus non-stricture group, Student's t, Mann-Whitney U, Chi-square, or Fisher exact tests were used as appropriate for data distribution. Multivariate logistic regression was used to estimate the exact odds ratio and its 95% lower confidence limit (LCL) of developing strictures for a risk factor of interest adjusted for age and sex. A 2-sided $p < 0.05$ was determined significant. Analyses were performed using IBM SPSS statistics version 25 for Windows (IBM, Inc, Somers, NY).

Results

A total of 222 EoE patients were seen between 01/2001 and 04/2021 and within them, 20 (9.1%) patients had strictures, all diagnosed at initial endoscopy. The stricture prevalence increased to 18.7% within the subgroup of patients with dysphagia. Sample demographics and clinical features for stricture versus non-stricture patients are given in Table 1. The mean age of the stricture patients at EoE diagnosis was 12.7 years (range 7-18) compared to the non-stricture patients which were 9.3 years (range 1-17) (p = 0.006). In two patient's strictures were "dilated" with the gentle passage of the regular endoscope (OD 9 mm) at diagnosis and was started on topical steroids three days later, when biopsies confirmed the diagnosis. The rest of the patients were pretreated with topical steroids for 4 - 6 weeks. On follow-up endoscopy, post topical steroid treatment 18 patients required dilation. Among the 20 patients with strictures, dysphagia and food impaction were significantly more prevalent: dysphagia was present in 100% of patients in the stricture group versus 41.6% in the non-stricture group (p < 0.0005) and food impaction was seen in 70% of stricture group *vs.* 4% in the non-stricture group (p < 0.0005).

Abdominal pain was noted more in the non-stricture group versus the stricture group; 31.2% *vs.* 5% (p = 0.017) respectively. Esophageal rings and exudates were seen significantly more in stricture patients compared with non-stricture patients, 45% *vs.* 4.5%, (p < 0.0005) and 60% *vs.* 30.7%, (p < 0.008), respectively. EGD and biopsy findings are given in Table 2. Differences between the stricture and non-stricture groups for the remaining symptoms and EGD findings were not significant. Eosinophil counts on biopsies, though higher in the stricture group, were not statistically significant. The choice of treatment and associated allergic diseases also did not show strong associations with either group. Multivariate logistic regression analysis confirmed that strictures were more likely to occur among those patients with dysphagia (p = 0.02, exact OR = 11.7, 95% LCL 2.0) and food impaction (p = 0.0001, exact OR = 80.9, 95% LCL 15.4), respectively, adjusted for age and gender.

Table 1: Demographics and Clinical Features.

	Stricture (n = 20)		Non-Stricture (n = 202)		
	n	%	n	%	p value
Demographics					
Age	12.7 +/- 4.29		9.4 +/- 5.12		0.006*
Male	15	75.0	162	80.2%	0.58^{++}
Presenting symptoms					
Dysphagia	20	100%	84	41.6	< 0.0005^{++}
Food Impaction	14	70.0%	8	4.0%	< 0.0005^{++}
Abdominal Pain	1	5.0%	63	31.2%	0.017^{+}
Vomiting/ GERD	2	10.0%	49	24.3%	0.18^{+}
FTT	0	0%	4	2.0%	1^{+}
Miscellaneous	0	0%	22	10.9%	0.23^{+}
Associated Allergies$^{\#}$	10	50.0%	79	39.1%	0.34^{++}
GI Bleeding	1	5.0%	2	1.0%	0.25^{+}

$^{\#}$Food allergy, seasonal allergy, atopic conditions *t-Test; $^{++}$ Chi-square test; $^{+}$Fisher's extract test

Table 2: EGD and Biopsy Findings.

	Stricture (n = 20)		Non-Stricture (n = 202)		
	n	%	n	%	p value
EGD					
Edema	8	40%	52	25.7%	0.17^{++}
Rings	9	45%	9	4.5%	< .0005^{++}
Exudates	12	60%	62	30.7%	0.008^{++}
Furrows	11	55%	110	54.5%	0.96^{++}
Stricture	20	100%	0	0	NA
Biopsy at diagnosis (median, 25% ile - 75% ile)					
Peak Eosinophil count/hpf	40	26.25 - 79.5	30	25 - 50	0.24°
Mean Eosinophil Count/hpf	35.5	20.63 - 70.88	30	22.5 - 50	0.57°
Distal$^{\#}$	40	21.25 - 78.75	30	25 - 50	0.35°
Mid$^{\#}$	40	17 - 62.25	30	20 - 50	0.44°

$^{++}$Chi-square test; $^{\circ}$Mann-Whitney U test. $^{\#}$Eosinophil/hpf

Discussion

Risk factors or determinants of disease are defined as those factors that lead to the development of a disease and are correlational but not necessarily causal [22], Known risk factors for the development of EoE are male gender, Caucasian race, habitat in colder climates, associated atopic disease, certain seasons of the year, early life exposure to antibiotics, cesarean delivery, preterm birth, and formula feeding during infancy [23]. Familial occurrence within siblings, parents, and twins have an increased risk based on gene analysis, but it is more likely related to living in a common environment [23]. EoE is not a uniform disease and has a number of subtypes that may respond differently to usual treatment [4]. It differs, according to age, presenting symptoms and inflammation, and whether the phenotype is inflammatory or structuring [24]. Current understanding of EoE is that the ongoing eosinophilic inflammation leads to remodeling, fibrosis, and eventually strictures [11,12]. Based on this model, EoE patients, if left untreated, likely will progress to fibrosis and strictures. This is supported by a cross-sectional study from Switzerland and another study from the USA [25,26] where adults with EoE and delayed treatment were more likely to have esophageal strictures, specifically if the delay in diagnosis was six or more years. Within this group of patients less than 20 years of age, the delay in diagnosis of EoE was around 10 years. The authors postulate the reason for this decade of delay in this mostly pediatric population, maybe because parents were concerned about having their child undergo an invasive diagnostic procedure requiring anesthesia and its associated risks [25]. If disease progression and or delay in treatment leads to stricture formation, then there should be fewer esophageal strictures in children compared to adults. The prevalence of strictures in adults varies from 7.7 and 9% based on two large EoE patient populations of 1019 and 513, respectively [25,27]. Another study by Eluri showed a higher stricture prevalence of 28% within a group of 776 EoE adults, although the authors did not give an explanation for the higher incidence [28]. Similar higher incidence, of 36% was shown in a study from the Netherlands [29]. However, in this study, the initial cohort of EoE patients was 2161 and the final analyzed group

was 721 patients, potentially confounding the true stricture incidence. Pediatric studies have shown a stricture prevalence of 6.3% among a cohort of 381, which is closer to our findings of 9.1% and another study with a prevalence of 22% among 50 EoE children [15,29]. The latter study was done in a region of high consanguinity and the authors postulate a genetic role may be the reason for the increased stricture incidence. In our study, the stricture prevalence was 9.1% among the total EoE population. However, our stricture prevalence increased to 18.7% when we selectively analyzed the 107 patients with dysphagia as the primary symptom, which is similar to findings in adult EoE studies with predominant dysphagia. These 107 patients were older and so did not include infants and toddlers, in whom dysphagia is difficult to assess, while the younger age group did not have strictures. These findings of stricture rate in children, almost similar to adults with EoE, raise the question if a delay in treatment leads to strictures or whether are there other factors that play a role in the development of strictures in children with EoE. Our database was designed based on Franciosi's data collection tool, which did not capture the duration of the symptoms at EoE diagnosis [19]. Based on the significant difference we found for the age of stricture diagnosis (12.7 years versus a non-stricture group of 9.4 years) in single and multivariate analyses, we suggest that this age difference may serve as a surrogate for the duration of symptoms. Thus, the duration of untreated disease may be a risk factor for the development of strictures in children. On the contrary, these patients live with observant parents or caregivers and so it is less likely, given the age group, that these symptoms were overlooked, and medical treatment delayed for as long a duration as was found in adults. Adults with EoE who self-monitor and make adjustments in their eating habits to overcome dysphagia have an average duration of symptoms before diagnosis of stricture of six or seven years [25,26]. Warners, et al. [29]. Reported a difference in the delayed period for stricture diagnosis for children (3.6 ± 4 years) compared to adults (7.2 ± 8.3 years). Our study confirms the age gap between those with and without stricture diagnosis was three years.

Symptomatology also appears to differ in our study of children with EoE compared to adult studies. Schoepher, et al. [25] showed that in adult patients with strictures, 100% had dysphagia compared to 80% in those without strictures. The stricture group also had a higher occurrence of food impaction (67%). Within our pediatric patients, we found that the stricture group reported 100% dysphagia, but only 42% had dysphagia in the non-stricture group. This gap was even wider with reported food impaction, 70% in the stricture group and 4% in the non-stricture group, which is a substantial difference compared to adult data. Lipka's study, in addition, to delay in diagnosis, looked at the use of aspirin, NSAIDs, tobacco, or alcohol in EoE adults with strictures. These on their own were not risk factors for strictures but became significant risk factors if in addition to their use there was a delay in the diagnosis of more than seven years [26]. Prior studies in adults with strictures did not find associated allergic diseases as a risk factor for stricture development and our data supports the same conclusion. While the co-occurrence of allergic disorders can increase blood eosinophilia, its impact on the manifestations of EoE including the severity of EoE and /or occurrence of stricture formation is difficult to establish with cross-sectional studies [12]. Gender was not different within the groups and there was male predominance in both groups, consistent with increased occurrence of EoE in males [1-3,29].

Endoscopic findings in the stricture group had a significant increase in the presence of esophageal rings and exudates, which is an observation supported by published data [25-28].

Exudates reflect increased eosinophilic inflammation and so we expected that the stricture group would have a higher eosinophil count. However, both groups had increased eosinophilic inflammation without a significant difference; this included the peak eosinophil count, mean eosinophil count, and also comparing distal versus mid-esophageal biopsies. Analysis of the types of treatment for both groups did not reveal a statistical difference.

While it was logical to expect dysphagia and or food impaction in patients with strictures, strikingly, abdominal pain was significantly more common in the non-stricture group. This raises the question of whether EoE patients presenting with abdominal pain without dysphagia are a different phenotypic group of EoE. If so, an interesting hypothesis is, would this group be protected from developing esophageal strictures? Our earlier study showed that children with EoE presenting predominantly with abdominal pain and without dysphagia compared to those presenting with dysphagia are different forms of EoE [21,30]. We do acknowledge that as per the Guidelines younger children present with abdominal pain [1,2].

Adult patients with EoE and strictures, fit into the fibrostenotic phenotype as they often have a long-standing disease with remodeling. Could this be the same in children with EoE and strictures? A study from the network of European countries looked at 410 children with EoE and only 7 (1.7%) patients required esophageal dilation [32]. Within that group of 410 children, 22 (5.3%) children required systemic steroids. The same group, in another study, from the same database, showed 20 children with esophageal strictures were treated with systemic steroids, at a mean dose of 1.4 mg/kg. On follow-up endoscopy, after a mean period of four weeks, in 19 patients the strictures improved, avoiding dilation [33]. This study supports, that strictures in children may be primarily inflammatory and may not be fibrostenotic. This conclusion is based on therapeutic response rather than evaluating mucosal biopsies for fibrosis. In our study, only two patients' strictures improved with topical steroids, and these two patients on follow-up required esophageal

dilation. The presence of fibrosis in mucosal biopsies would help differentiate the phenotype of these strictures, but the challenge is, in only about 50% of the biopsies are evaluable for fibrosis. Hence using the novel technique, EndoFLIP, which evaluates the esophageal distensibility, in children, would help delineate the phenotype of strictures in EoE and should be considered for future studies [34]. Within the non-stricture group 84 (41.6%) and eight (4%) patients had dysphagia and food impaction respectively. Based on our conclusion these patients, though had no strictures, are at risk of developing strictures. We do not have clear guidelines to predict if they will develop strictures, but it's prudent to follow these patients more closely.

Limitations of our study are its retrospective nature and the inability to capture the duration of the symptoms prior to diagnosis from the medical record. With recent Guidelines not requiring prior PPI treatment for a diagnosis of EoE, it is possible we may have missed including some patients in the study. Our clinic practice of EoE diagnosis was to have a negative pH study and most of the study patients belonged to this group or were diagnosed with 2018 Guidelines, of not requiring PPI pretreatment, so the missed patients may not be many. Also, we did not compare the mucosal biopsies for fibrosis within the groups to differentiate fibrostenotic versus inflammatory strictures or use EndoFLIP. These limitations are mitigated by the strengths of the study, which include a large and well-characterized cohort of EoE patients, that systematically analyzed patients' symptoms and endoscopic findings and histology in both groups. To our knowledge, this is the first study on children to look at the risk factors associated with esophageal strictures in children and adolescents with EoE.

In conclusion, EoE children and adolescents presenting with dysphagia or food impaction, and having exudates and rings on endoscopy, should be considered as risk indicators for having esophageal strictures compared to those without these features. Additionally, pediatric EoE patients typically present with strictures after 12 years of age. Thus, we suggest EoE children 12 years or older presenting with dysphagia or food impaction who have esophageal exudates or rings on endoscopy should be treated and closely monitored to reduce stricture formation. Additional prospective case-controlled studies, with the inclusion of EndoFLIP, are required to support or challenge our findings.

References

1. Dellon ES, Liacouras CA, Molina-Infante J, Furuta GT, Spergel JM, et al. Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the AGREE Conference. Gastroenterology. 2018 Oct;155(4):1022-1033.e10. doi: 10.1053/j.gastro.2018.07.009. Epub 2018 Sep 6. PMID: 30009819; PMCID: PMC6174113.

2. Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol. 2011 Jul;128(1):3-20.e6; quiz 21-2. doi: 10.1016/j.jaci.2011.02.040. Epub 2011 Apr 7. PMID: 21477849.

3. Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, Bonis P, Hassall E, Straumann A, Rothenberg ME; 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 Oct;133(4):1342-63. doi: 10.1053/j.gastro.2007.08.017. Epub 2007 Aug 8. PMID: 17919504.

4. Baker RD, Baker SS. Towards Better Diagnosis and Monitoring of Eosinophilic Esophagitis: Are We There Yet? J Pediatr Gastroenterol Nutr. 2020 Apr;70(4):410. doi: 10.1097/MPG.0000000000002603. PMID: 31880661.

5. Dellon ES, Jensen ET, Martin CF, Shaheen NJ, Kappelman MD. Prevalence of eosinophilic esophagitis in the United States. Clin Gastroenterol Hepatol. 2014 Apr;12(4):589-96.e1. doi: 10.1016/j.cgh.2013.09.008. Epub 2013 Sep 11. PMID: 24035773; PMCID: PMC3952040.

6. Soon IS, Butzner JD, Kaplan GG, deBruyn JC. Incidence and prevalence of eosinophilic esophagitis in children. J Pediatr Gastroenterol Nutr. 2013 Jul;57(1):72-80. doi: 10.1097/MPG.0b013e318291fee2. PMID: 23539047..

7. Odze RD. Pathology of eosinophilic esophagitis: what the clinician needs to know. Am J Gastroenterol. 2009 Feb;104(2):485-90. doi: 10.1038/ajg.2008.40. Epub 2009 Jan 13. PMID: 19174804.

8. Straumann A, Bauer M, Fischer B, Blaser K, Simon HU. Idiopathic eosinophilic esophagitis is associated with a T(H)2-type allergic inflammatory response. J Allergy Clin Immunol. 2001 Dec;108(6):954-61. doi: 10.1067/mai.2001.119917. PMID: 11742273.

9. Rawson R, Yang T, Newbury RO, Aquino M, Doshi A, Bell B, Broide DH, Dohil R, Kurten R, Aceves SS. TGF-β1-induced PAI-1 contributes to a profibrotic network in patients with eosinophilic esophagitis. J Allergy Clin Immunol. 2016 Sep;138(3):791-800.e4. doi: 10.1016/j.jaci.2016.02.028. Epub 2016 Apr 8. PMID: 27212082; PMCID: PMC5014565.

10. Yang ZC, Yi MJ, Ran N, Wang C, Fu P, Feng XY, Xu L, Qu ZH. Transforming growth factor-β1 induces bronchial epithelial cells to mesenchymal transition by activating the Snail pathway and promotes airway remodeling in asthma. Mol Med Rep. 2013 Dec;8(6):1663-8. doi: 10.3892/mmr.2013.1728. Epub 2013 Oct 14. PMID: 24126595.

11. Kagalwalla AF, Akhtar N, Woodruff SA, Rea BA, Masterson JC, Mukkada V, Parashette KR, Du J, Fillon S, Protheroe CA, Lee JJ, Amsden K, Melin-Aldana H, Capocelli KE, Furuta GT, Ackerman SJ. Eosinophilic esophagitis: epithelial mesenchymal transition contributes to esophageal remodeling and reverses with treatment. J Allergy Clin Immunol. 2012 May;129(5):1387-1396.e7. doi: 10.1016/j.jaci.2012.03.005. Epub 2012 Apr 1. PMID: 22465212; PMCID: PMC3340537.

12. Aceves SS. Remodeling and fibrosis in chronic eosinophil inflammation. Dig Dis. 2014;32(1-2):15-21. doi: 10.1159/000357004. Epub 2014 Feb 28. PMID: 24603375; PMCID: PMC4037288.

13. Hirano I, Pandolfino JE, Boeckxstaens GE. Functional lumen imaging probe for the management of esophageal disorders: expert review from the Clinical Practice Updates Committee of the AGA Institute. Clin Gastroenterol Hepatol. 2017; 15: 325-334.

14. Dellon ES, Kim HP, Sperry SL, Rybnicek DA, Woosley JT, Shaheen NJ. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. Gastrointest Endosc. 2014 Apr;79(4):577-85.e4. doi: 10.1016/j.gie.2013.10.027. Epub 2013 Nov 23. PMID: 24275329; PMCID: PMC4599711.

15. Kim JP, Weingart G, Hiramoto B, Gregory DL, Gonsalves N, Hirano I. Clinical outcomes of adults with eosinophilic esophagitis with severe stricture. Gastrointest Endosc. 2020 Jul;92(1):44-53. doi: 10.1016/j.gie.2020.01.015. Epub 2020 Jan 16. PMID: 31954704.

16. Al-Hussaini A. Savary Dilation Is Safe and Effective Treatment for Esophageal Narrowing Related to Pediatric Eosinophilic Esophagitis. J Pediatr Gastroenterol Nutr. 2016 Nov;63(5):474-480. doi: 10.1097/MPG.0000000000001247. PMID: 27111342; PMCID: PMC5084639.

17. Gunasekaran T, Kory V, Li Y.Esophageal Strictures in Pediatric Patients with Eosinophilic Esophagitis; Short Segment Stricture Vs. Narrow Caliber Esophagus. SF Hepatology Gastroenterology 2020; 1(1):1003. https://scienceforecastoa.com/Articles/HG-V1-E1-1003.pdf

18. Gunasekaran T, Kory V, Sonawane SS.Comprehensive Comparison of Dysphagia Predominant Eosinophilic Esophagitis, with and without Food Impaction: 101 Children and Adolescents. SN Compr. Clin. Med. 2021;3: 2134-2140. https://doi.org/10.1007/s42399-02100889-1

19. Franciosi JP, Hommel KA, DeBrosse CW, Greenberg AB, Greenler AJ, Abonia JP, Rothenberg ME, Varni JW. Development of a validated patient-reported symptom metric for pediatric eosinophilic esophagitis: qualitative methods. BMC Gastroenterol. 2011 Nov 18;11:126. doi: 10.1186/1471-230X-11-126. PMID: 22099448; PMCID: PMC3228698.

20. Dohil R, Newbury R, Fox L, Bastian J, Aceves S. Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. Gastroenterology. 2010 Aug;139(2):418-29. doi: 10.1053/j.gastro.2010.05.001. Epub 2010 May 7. PMID: 20457157.

21. Gunasekaran T, Prabhakar G, Schwartz A, Gorla K, Gupta S, Berman J. Eosinophilic Esophagitis in Children and Adolescents with Abdominal Pain: Comparison with EoE-Dysphagia and Functional Abdominal Pain. Can J Gastroenterol Hepatol. 2016;2016:4123692. doi: 10.1155/2016/4123692. Epub 2016 Aug 16. PMID: 27610357; PMCID: PMC5004036.

22. Gunasekaran TS, Chu C, Ronquillo N Jr, Chennuri R, Adley B, Borgen K, Schwartz A, Newberry R, Berman J. Detailed Histologic Evaluation of Eosinophilic Esophagitis in Pediatric Patients Presenting with Dysphagia or Abdominal Pain and Comparison of the Histology between the Two Groups. Can J Gastroenterol Hepatol. 2017;2017:3709254. doi: 10.1155/2017/3709254. Epub 2017 Dec 17. PMID: 29392125; PMCID: PMC5748089.

23. Arias Á, Lucendo AJ. Epidemiology and risk factors for eosinophilic esophagitis: lessons for clinicians. Expert Rev Gastroenterol Hepatol. 2020 Nov;14(11):1069-1082. doi: 10.1080/17474124.2020.1806054. Epub 2020 Aug 24. PMID: 32749898.

24. Ferguson AE, Fulkerson PC. Eosinophilic esophagitis: Time to classify into endotypes? J Allergy Clin Immunol. 2018 Jul;142(1):71-72. doi: 10.1016/j.jaci.2018.04.025. Epub 2018 May 8. PMID: 29751005; PMCID: PMC8034426.

25. Schoepfer AM, Safroneeva E, Bussmann C, Kuchen T, Portmann S, Simon HU, Straumann A. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. Gastroenterology. 2013 Dec;145(6):1230-6.e1-2. doi: 10.1053/j.gastro.2013.08.015. Epub 2013 Aug 13. PMID: 23954315.

26. Lipka S, Kumar A, Richter JE. Impact of Diagnostic Delay and Other Risk Factors on Eosinophilic Esophagitis Phenotype and Esophageal Diameter. J Clin Gastroenterol. 2016 Feb;50(2):134-40. doi: 10.1097/MCG.0000000000000297. PMID: 25710524.

27. Kim JP, Weingart G, Hiramoto B, Gregory DL, Gonsalves N, Hirano I. Clinical outcomes of adults with eosinophilic esophagitis with severe stricture. Gastrointest Endosc. 2020 Jul;92(1):44-53. doi: 10.1016/j.gie.2020.01.015. Epub 2020 Jan 16. PMID: 31954704.

28. Eluri S, Tappata M, Huang KZ, Koutlas NT, Robey BS, Fan C, Reed CC, Shaheen NJ, Dellon ES. Distal esophagus is the most commonly involved site for strictures in patients with eosinophilic esophagitis. Dis Esophagus. 2020 Mar 5;33(2):doz088. doi: 10.1093/dote/doz088. PMID: 31778150 .

29. Warners MJ, Oude Nijhuis RAB, de Wijkerslooth LRH, Smout AJPM, Bredenoord AJ. The natural course of eosinophilic esophagitis and long-term consequences of undiagnosed disease in a large cohort. Am J Gastroenterol. 2018 Jun;113(6):836-844. doi: 10.1038/s41395-018-0052-5. Epub 2018 Apr 27. PMID: 29700481.

30. Gunasekaran TS, Chu C, Ronquillo N Jr, Chennuri R, Adley B, Borgen K, Schwartz A, Newberry R, Berman J. Detailed Histologic Evaluation of Eosinophilic Esophagitis in Pediatric Patients Presenting with Dysphagia or Abdominal Pain and Comparison of the Histology between the Two Groups. Can J Gastroenterol Hepatol. 2017;2017:3709254. doi: 10.1155/2017/3709254. Epub 2017 Dec 17. PMID: 29392125; PMCID: PMC5748089.

31. Liacouras CA, Spergel JM, Ruchelli E, Verma R, Mascarenhas M, Semeao E, Flick J, Kelly J, Brown-Whitehorn T, Mamula P, Markowitz JE. Eosinophilic esophagitis: a 10-year experience in 381 children. Clin Gastroenterol Hepatol. 2005 Dec;3(12):1198-206. doi: 10.1016/s1542-3565(05)00885-2. PMID: 16361045.

32. Hoofien A, Dias JA, Malamisura M, Rea F, Chong S, Oudshoorn J, Nijenhuis-Hendriks D, Otte S, Papadopoulou A, Romano C, Gottrand F, Miravet VV, Orel R, Oliva S, Junquera CG, Załęski A, Urbonas V, Garcia-Puig R, Gomez MJM, Dominguez-Ortega G, Auth MK, Kori M, Ben Tov A, Kalach N, Velde SV, Furman M, Miele E, Marderfeld L, Roma E, Zevit N. Pediatric Eosinophilic Esophagitis: Results of the European Retrospective Pediatric Eosinophilic Esophagitis Registry (RetroPEER). J Pediatr Gastroenterol Nutr. 2019 Apr;68(4):552-558. doi: 10.1097/MPG.0000000000002215. PMID: 30540712.

33. Hoofien A, Rea F, Espinheira MDC, Amil Dias J, Romano C, Oliva S, Auth MK, Zangen T, Kalach N, Domínguez-Ortega G, De Angelis P, Zevit N; ESPGHAN EGID Working Group. Systemic steroids have a role in treating esophageal strictures in pediatric eosinophilic esophagitis. Dig Liver Dis. 2021 Mar;53(3):324-328. doi: 10.1016/j.dld.2020.11.025. Epub 2020 Dec 15. PMID: 33334703.

34. Menard KC, Benitez A, Pan Z, Faria A .Influence of age and esosinophilic esophagitis in esophageal distensibility in pediatric cohort. Am J Gastroenterol 2017; 112:1466-1473.