Is There a Role for pH Impedance Monitoring in Identifying Eosinophilic Esophagitis in Children with Esophageal Atresia?

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Objectives To evaluate clinical, endoscopic, and pH-impedance measures in a cohort of children with esophageal atresia and concomitant eosinophilic esophagitis (EoE) and compared it with disease-matched controls, to identify predictive factors for the development of EoE and esophageal stricture.

Study design We reviewed 63 patients with esophageal atresia assessed for refractory upper gastrointestinal symptoms between January 2015 and September 2017 at 2 tertiary referral centers. All patients underwent upper gastrointestinal endoscopy and pH-impedance monitoring. Based on esophageal histology, patients were classified as (1) esophageal atresia without evidence of esophagitis; (2) esophageal atresia with evidence of esophagitis (including esophageal eosinophilia not meeting the criteria for EoE); (3) esophageal atresia with concomitant EoE. Age and sex matched patients with gastroesophageal reflux disease were used as disease controls.

Results The presence of atopy and peripheral eosinophilia at baseline were significantly associated with EoE ($P < .05$). Although there was a tendency toward an increased number of strictures in patients with esophageal atresia-EoE, this did not reach statistical significance ($P = .06$). Higher esophageal acid exposure time and lower baseline impedance values were significantly associated with eosinophilic infiltration ($P < .05$ and $P < .01$, respectively). Using logistic regression analysis, the presence of mucosal eosinophilia was the most predictive factor for stricture formation ($P < .05$).

Conclusions A history of atopy and the presence of peripheral eosinophilia in patients with esophageal atresia are predictive factors for the development of EoE, which in turn is a predictive factor for stricture occurrence. Higher esophageal acid exposure time and lower baseline impedance are associated with esophageal eosinophilic infiltration, suggesting their value in selecting which patients with esophageal atresia should undergo endoscopic examination. *(J Pediatr 2019;210:134-40)*.

Esophageal atresia, with or without trachea-esophageal fistula, is the most common congenital anomaly of the gastrointestinal (GI) tract and, given the increasingly successful surgical outcomes, it currently represents a lifelong issue.[1-3] All children with esophageal atresia have a variable degree of residual GI morbidity, and it is not uncommon for them to undergo many surgical procedures, including multiple esophageal dilatations and fundoplication.[4-6]

In the last few years, a higher prevalence of eosinophilic esophagitis (EoE) has been reported in children with esophageal atresia.[7-11] The diagnosis of EoE in esophageal atresia patients is often challenging due to the symptom overlap with refractory gastroesophageal reflux disease (GERD) as well as the distinctive presence of residual dysphagia because of esophageal dysmotility.[12,13] Hence, a delayed diagnosis of concomitant EoE is not uncommon. This delay might put children at a risk of unnecessary diagnostic and therapeutic interventions in the interim or conversely developing complications from untreated EoE. Currently, there is limited evidence on how to stratify patients' risk of having concomitant EoE in the esophageal atresia population.

The aim of this retrospective study was to assess whether clinical, endoscopic, and pH-impedance measures are able to identify children with esophageal atresia at risk of having concomitant EoE and, therefore, potentially influence clinical management.

AET	Acid exposure time
EoE	Eosinophilic esophagitis
GI	Gastrointestinal
GERD	Gastroesophageal reflux disease
hpf	High power field
PPIs	Proton pump inhibitors
MII-pH	Multichannel intraluminal impedance and pH

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Methods

A detailed retrospective chart review of all children with esophageal atresia referred consecutively either for refractory upper GI symptoms or as part of surveillance program between January 2015 and September 2017 to the Pediatric Gastroenterology Divisions of Sydney Children's Hospital (Sydney, Australia) and Neurogastroenterology and Motility Service at Great Ormond Street Hospital in London (London, United Kingdom) was performed. Children were investigated by means of esophageal 24-hour pH-impedance monitoring off-therapy and upper GI endoscopy to identify the underlying mechanisms of symptoms and to inform further clinical management. Before the investigations, none of the children had received acid suppression therapy or drugs affecting lower esophageal sphincter function (eg, b-adrenergic agonist or theophylline) for at least 7 days. During the anesthesia at the time of the endoscopic assessment, blood samples were routinely taken to assess the presence of peripheral eosinophilia.

The Research and Development Office of both Great Ormond Street Hospital and Sydney Children's Hospital approved the review of clinical records for the research proposed in this study.

Clinical Measures

In all patients, a detailed clinical history was obtained and parental reported symptoms were noted. These included dysphagia, reflux symptoms, cyanotic episodes, and food bolus impaction. Other clinical variables recorded included (1) predominant symptoms at presentation, (2) timing of symptom onset after atresia repair, (3) personal and familiar history of atopy and presence of peripheral eosinophilia, (4) type of esophageal atresia, (5) presence, number, and timing of esophageal strictures needing dilation, and (6) number, type, and timing of surgical interventions (including fundoplication and gastrostomies). The type of esophageal atresia was defined according to the Gross classification, whereas long gap esophageal atresia was defined as any distance (>2 vertebral bodies) between the esophageal (pouch) ends in a newborn too wide for a primary anastomosis.[14,15] In the esophageal atresia-EoE group, the number of strictures and dilatations and the clinical outcomes after the diagnosis of EoE were also recorded.

Endoscopic Assessment

The diagnosis of concomitant EoE was based on standardized diagnostic criteria: (1) at least one baseline esophageal biopsy demonstrating a peak eosinophil count ≥15/high power field (HPF); (2) use of proton pump inhibitors (PPIs) prior to diagnosis of EoE and at time of diagnosis of EoE.[12]

All EoE patients included in the study had documented endoscopies and biopsies performed at baseline diagnosis and subsequent follow-up. In all patients, the presence of chronic noneosinophilic driven histologic changes (ie, basal cell hyperplasia, lamina propria elongation, spongiosis, parakeratosis, and subepithelial hyalinization) was also recorded.

pH-Impedance Monitoring

All children underwent 24-hour multichannel intraluminal impedance and pH (MII-pH) monitoring within 1 week of the endoscopic assessment. In all patients, off-therapy 24-hour ambulatory esophageal MII-pH monitoring was performed using a Sleuth Multi-Channel Intraluminal Impedance ambulatory system (Sleuth, Sandhill Scientific, Inc; Highland Ranch, Colorado). The study was performed according to standardized protocol and probe position was confirmed with a chest radiograph.[16]

The data collected were visually analyzed with the assistance of dedicated software (Bioview Analysis, v 5.0.9; Sandhill Scientific, Inc). Analysis included identification, enumeration, and characterization of reflux events, proximal propagation of reflux episodes, acid exposure time (AET), and symptom association probability.[16] Esophageal AET was calculated as the percentage of time the intraesophageal pH dropped pH < 4 during the recording period as previously described.[16] In all patients, intraluminal baseline impedance values were recorded according to standardized methodology.[17] Briefly, baseline impedance levels were assessed in 2 distal (channels 5 and 6) impedance channels, and automatically calculated every 4 hours over the first stable minute-period, when neither reflux episodes or swallowing were present, by a specific software function (electronic ruler). Subsequently, the 4 hourly baseline impedance values obtained from the complete tracing were averaged to obtain the mean baseline values for the entire recording.[17,18]

Study Protocol and Statistical Analyses

Based on the results of the endoscopies, esophageal atresia patients were then divided into 3 groups: (1) patients with esophageal atresia without evidence of esophagitis (esophageal atresia group); (2) patients with esophageal atresia with histologic evidence of esophagitis (esophageal eosinophilia at endoscopic biopsies, not meeting the criteria for EoE (esophageal atresia-eosinophilia group, <15 eosinophils/hpf); and (3) patients with esophageal atresia with concomitant EoE (esophageal atresia-EoE group, >15 eosinophils/hpf). Only children who underwent 24-hour MII-pH monitoring off-PPIs therapy were included in the final analysis.

Ten sex- and age-matched patients (mean age 8.9 ± 7.5 years, 4 male patients) undergoing pH impedance and endoscopic investigations for GERD symptoms were included as controls. None of them had a history of atopy and/or presence of peripheral eosinophilia.

Patient and disease characteristics are expressed as median (range) and mean ± SD, dependent on the normality of the distribution as assessed with Kolmogorov-Smirnov test. Comparisons between groups for continuous variables were performed using ANOVA, whereas Wilcoxon signed-rank test and Mann-Whitney U test were used when appropriate. Categorical variables were compared using χ^2 or the Fisher

exact test as appropriate. Furthermore, the adjusted effect of different factors on the outcomes (ie, disease phenotype and stricture formation, respectively) was explored using logistic regression and Cox regression analysis. Statistical analysis was performed with SPSS v 17.0 software (SPSS Inc, Chicago, Illinois). Statistical significance was set at the $P < .05$ level.

Results

Clinical and Demographic Characteristics

Over a period of 32 months, 72 children were considered eligible for the study, of which 9 were excluded from the final analysis either because there were insufficient data available to determine disease phenotype (high anesthetic risk to undergo the investigations in 2 patients and either failure to pass the pH probe or malfunction of the MII-pH monitoring system during the recording in 5 patients), or on treatment with PPI during the pH-impedance study (2 patients). Analysis was, therefore, completed in 63 patients (median age 7 years, range 1-22 years, 38 male patients), and according to histologic phenotype patients were divided into three subgroups: (1) 24 patients with esophageal atresias; (2) 20 patients with esophageal atresia-eosinophilia; and (3) 19 patients with esophageal atresia-EoE.

Table I summarizes the clinical and demographic characteristics of the study groups. Fifty-one children with esophageal atresia (80.9%) had type C defects, whereas the remaining 14.3% had type A defects. Three children had long-gap defects, whereas associated congenital defects were reported in 66% of the overall population and ranged from isolated cardiac/vertebral/anal defects to the VACTERL (vertebral, anorectal, cardiac, tracheoesophageal, renal, limb defects) association. None of the reported symptoms and signs could discriminate between the 3 groups at baseline evaluation (Table I). In addition, no significant differences between groups were found in the frequency of gastrostomy tubes or of previous antireflux surgery. Moreover, although there was a tendency toward an increased number of strictures in the esophageal atresia-EoE group, it did not reach statistical significance ($P = .06$). Neither the presence, the type (anastomotic vs nonanastomotic) or the timing of strictures (early vs late) nor the presence of recurrent vs isolated strictures differed among groups (Table I). The only factors that were found to be significantly more frequent in children with esophageal atresia-EoE compared with the other 2 groups were the presence of atopy and peripheral eosinophilia (both $P < .05$ by ANOVA) (Table I).

Table I. Demographic and clinical characteristics of the 3 groups of patients with esophageal atresia

Variables	Esophageal atresia	Esophageal atresia-eosinophilia*	Esophageal atresia-EoE†
Number of cases	24	20	19
Age (y; median and ranges)	8.94 (1-21)	7.95 (1-22)	6.68 (1-15)
Male/female (number and percentage)	13/9 (54%)	12/8 (60%)	13/6 (68%)
Type of atresia (number and percentage)			
Type C	19 (80%)	16 (80%)	16 (84%)
Type A	5 (20%)	3 (15%)	1 (5%)
Long gap atresia	-	1 (5%)	2 (10%)
Associated congenital abnormalities (number and percentage)			
VACTERL association	5/24 (21%)	5/20 (25%)	3/19 (16%)
Cardiac abnormalities	6/24 (25%)	6/20 (30%)	-
Vertebral abnormalities	1/24 (4%)	5/20 (25%)	1/19 (5%)
Anal anomalies	6/24 (25%)	2/20 (10%)	2/19 (10%)
Symptoms and signs (number and percentage)			
Asymptomatic	5/24 (21%)	2/20 (10%)	5/19 (26%)
Regurgitation/vomiting	9/24 (37.5%)	12/20 (60%)	5/19 (26%)
Pyrosis	6/24 (25%)	8/20 (40%)	2/19 (10%)
Epigastric pain	1/24 (4%)	0/20 (0%)	0/19 (0%)
Hematemesis	0/24 (0%)	0/20 (0%)	0/19 (0%)
Cough	9/24 (37.5%)	2/20 (10%)	5/19 (26%)
Recurrent pneumonia	9/24 (37.5%)	3/20 (15%)	2/19 (10%)
Dysphagia	15/24 (62.5%)	16/20 (80%)	13/19 (68%)
Eating difficulties	5/24 (21%)	4/20 (20%)	5/19 (26%)
Reactive airway disease	5/24 (21%)	3/20 (7%)	9/19 (47%)
Cyanotic spells	3/24 (12%)	1/20 (5%)	1/19 (5%)
History of atopy	4/24 (16%)	5/20 (25%)	8/19 (42%)‡
Peripheral eosinophilia	1/24 (4%)	3/20 (15%)	8/19 (42%)‡
Gastrostomy	8/24 (33%)	7/20 (35%)	6/19 (31%)
History of fundoplication	8/24 (33%)	4/20 (20%)	5/19 (26%)
Presence of strictures‡ (number and percentage)			
Past history of stricture	11/24 (46%)	12/20 (60%)	13/19 (68%)
Anastomotic strictures	6/24 (25%)	8/20 (40%)	8/19 (42%)
Early strictures	5/24 (21%)	8/20 (40%)	3/19 (16%)
Recurrent strictures	9/24 (37.5%)	9/20 (45%)	7/19 (37%)

hpf, high power field; *VACTERL*, vertebral, anorectal, cardiac, tracheoesophageal, renal, limb defects.
*Esophageal eosinophilia not meeting the criteria for EoE (<15 eosinophils/hpf).
†Esophageal eosinophilia meeting the criteria for EoE (<15 eosinophils/hpf).
‡$P < .05$ vs both esophageal atresia and esophageal atresia/eosinophilia.

Table II. pH-impedance parameters in esophageal atresia, esophageal atresia-eosinophilia, esophageal atresia-EoE, GERD, and EoE groups

pH-impedance parameters	Esophageal atresia	Esophageal atresia -eosinophilia*	Esophageal atresia-EoE†	GERD	EoE
Number of cases	24	20	19	10	10
Esophageal AET(%) (mean ± SD)	3 ± 2.9‡	5.6 ± 4.8	8.6 ± 6.07	4.4 ± 1.9	2.69 ± 3.7
Total number of reflux episodes (mean ± SD)	43 ± 39.7	32 ± 39	58 ± 37	36 ± 23	34.9 ± 30
Number of acid reflux episodes (mean ± SD)	15 ± 24	30 ± 21	25 ± 21	21 ± 15	19.3 ± 14.4
Weakly acid reflux episodes (mean ± SD)	28 ± 22	6 ± 10	29.4 ± 29	22 ± 15	14.5 ± 15.7
Weakly alkaline reflux episodes (mean ± SD)	27 ± 21	21 ± 10	31.3 ± 27	4 ± 0.9	1 ± 2.1
Baseline impedance (Ohm) (mean ± SD)	1371 ± 632§	1576 ± 789§	708 ± 265	1832 ± 759¶	1862 ± 860¶

*Esophageal eosinophilia not meeting the criteria for EoE (<15 eosinophils/hpf).
†Esophageal eosinophilia meeting the criteria for EoE (<15 eosinophils/hpf).
‡$P < .05$ vs EoE.
§$P < .05$ vs esophageal atresia-EoE.
¶$P < .01$ vs esophageal atresia-EoE.

pH Impedance Measures

Table II summarizes the pH-impedance measures among the study groups. Esophageal atresia-EoE group showed a significantly greater percentage of AET compared with the esophageal atresia group ($P < .01$). Conversely, no differences were found between the esophageal atresia-EoE group and either the esophageal atresia-eosinophilia, GERD or EoE groups or between the esophageal atresia group and either the esophageal atresia-eosinophilia, GERD or EoE groups (Table II and Figure, A). Moreover, no other significant differences in terms of total number of reflux episodes, number of acid, weakly acidic, and nonacid reflux episodes were found between any of the patient groups (Table II).

The mean baseline impedance values in the whole esophageal atresia population (1231 ± 662) were significantly lower compared with either patients with GERD (1832 ± 759, $P < .05$) or patients with EoE (1862 ± 860, $P < .05$) without a past history of atresia repair. Comparing the baseline impedance values among the groups, patients with esophageal atresia-EoE showed significantly lower baseline impedance values compared with other groups (esophageal atresia: $P < .05$; esophageal atresia-eosinophilia: $P < .05$; GERD: $P < .01$; EoE: $P < .01$), whereas no differences were found among patients with esophageal atresia, esophageal atresia-eosinophilia, GERD, and EoE (Table II and Figure, B).

Regression Model

Linear and logistic regression analyses were used to identify predictors of EoE and stricture formation in the whole cohort of patients with esophageal atresia. The adjusted effect of various factors on the presence of concomitant EoE and the formation of strictures is depicted in Table III, respectively. Logistic regression analysis showed that the presence of peripheral eosinophilia was the most predictive factor for the concomitant presence of EoE, whereas the most predictive factor associated with stricture formation among the considered variables was the presence of eosinophilic infiltration in esophageal mucosal biopsies. In the in the whole cohort of children with esophageal atresia, there was no correlation between any symptom and both pH-impedance and endoscopic findings.

Treatment Outcome and Long-Term Follow-Up

Nineteen patients with esophageal atresia were identified and managed as per the most recent European Society for Pediatric Gastroenterology, Hepatology, and Nutrition EoE guidelines.[12] All patients underwent a repeat endoscopy after pharmacotherapy and/or elimination diet to verify the

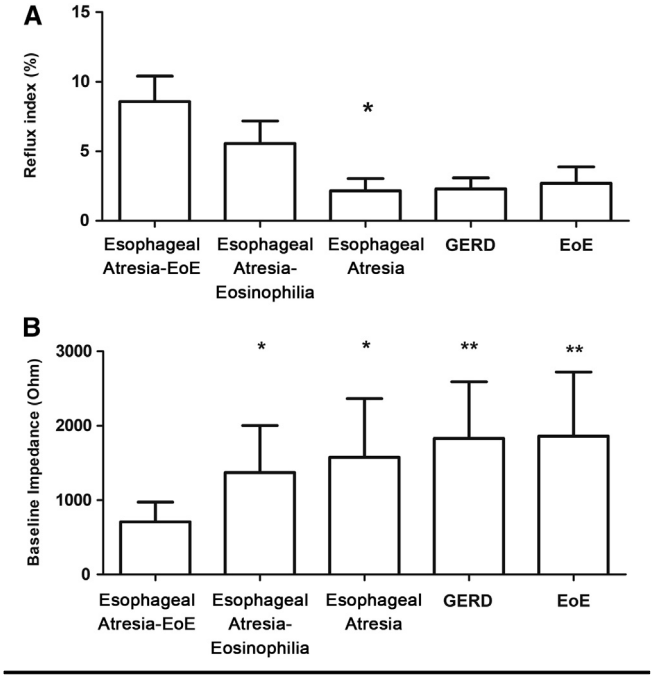

Figure. Differences in esophageal **A,** acid exposure (%) and **B,** baseline impedance values (Ohm) among the study groups: esophageal atresia; esophageal atresia-eosinophilia, esophageal eosinophilia not meeting the criteria for EoE (<15 eosinophils/hpf); esophageal atresia-EoE, esophageal eosinophilia meeting the criteria for EoE (>15 eosinophils/hpf); GERD; and EoE. *$P < .05$; **$P < .01$.

Table III. Adjusted effect of different variables on the diagnosis of EoE and on stricture formation (logistic regression model)

Covariates	HR	95% CI	*P* value
Diagnosis of EoE			
EAT	1.058	0.95-1.77	.298
Age	.866	0.66-1.12	.286
Peripheral eosinophilia	.041	0.03-0.55	.016
Stricture	.063	0.03-1.35	.077
Sex	1.270	015-10.5	.825
Stricture formation			
EAT	.983	0.9-1.07	.684
Age	.973	0.88-1.07	.567
Sex	.787	0.18-3.3	.746
Eosinophils/hpf	1.085	1-1.175	.046

EAT, esophageal acid exposure time; *HR*, hazard ratio.

resolution of the previously abnormal endoscopic and histopathologic findings. The mean follow-up was 22 months. The treatment regimen was PPI + budesonide in 15 of 19 patients, PPIs and diet in 4 of 19 patients. The elimination diet utilized was the empiric 6-food elimination diet (ie, soy, egg, milk, wheat, nuts, and seafood free diet) and was not performed on the basis of specific allergy tests (skin prick testing or patch testing). In all patients, EoE remission was histologically proven. Following therapy, all examined patients reported symptomatic improvement and none of those (7 of 19) with recurrent history of strictures had new episodes of food bolus impaction and/or strictures recurrence at follow-up.

Discussion

Recent case series have suggested an increased incidence of EoE in patients with esophageal atresia.[7-11] We evaluated patients with esophageal atresia with concomitant EoE and compared it with disease-matched controls, to identify predictive factors for EoE and stricture formation in this population. We found that a positive history of atopy and the presence of peripheral eosinophilia at baseline were significant associated with the occurrence of EoE. Also, we report for the first time that pH impedance measures are significantly associated with the presence of mucosal eosinophilic infiltration of esophageal biopsies. In particular, esophageal acid exposure time (AET) and baseline impedance values were significantly higher and lower, respectively, in the group of children with esophageal atresia with concomitant EoE. Finally, we found that the presence of mucosal eosinophilia was the most predictive factor for stricture formation.

Previous reports have evaluated baseline impedance in patients with esophageal atresia, demonstrating that the lower baseline impedance values are also related to esophageal dysmotility.[17] In our population, the baseline impedance values of the whole population of patients with esophageal atresia were significantly lower when compared with nondysmotile patients with GERD. However, when comparing patients with esophageal atresia and esophageal atresia with concomitant EoE, the baseline impedance appeared to be inversely related with the presence of mucosal eosinophilic infiltration. It must be noted that this effect could be related to the presence of mucosal inflammation as well as to the increased AET values observed in this group.[19-22] Increased AET was indeed significantly related to EoE. This finding is of particular interest because it attests that these patients are at increased risk of having pathological pH-impedance investigations, thus, exposing them to the risk of being misdiagnosed of having GERD rather than having concomitant EoE.[23-27] In line with these data stands the evidence that nearly 1 in 4 patients, including the esophageal atresia-EoE group, had already undergone an antireflux surgery at baseline evaluation.

Patients with esophageal atresia-EoE were described to be at increased risk of stricture formation.[9-11,28] Although there was a tendency toward an increased number of strictures in the esophageal atresia-EoE group, we failed to find any significant statistical difference in the number, type (anastomotic vs nonanastomotic) and timing (early vs late) of strictures. However, when comparing the different variables using a logistic regression model, the presence of mucosal eosinophilia was the most predictive factor for stricture formation. Further confirming the impact of mucosal eosinophilia on the formation of strictures, we also demonstrated that all patients with esophageal atresia-EoE did not have a relapse of stricture following specific therapy for EoE at a 22-month follow-up, pinpointing the impact of EoE therapy on the natural history of these patients. However, these outcomes must be carefully interpreted because of the small sample-size, the nonhomogeneous treatment regimens and their potential efficacy on esophageal complication, and the retrospective nature of our data. Nonetheless, from a pathophysiological standpoint, the use of topical corticosteroids in EoE has been proven to reverse the subepithelial fibrotic process, and hence, in patients with recurrent strictures might prevent their recurrence.[12,29-31] Similarly to that reported by Dhaliwal et al, all patients with esophageal atresia-EoE with strictures at baseline had showed endoscopic and symptomatic response to topical corticosteroids, supporting the inflammatory nature of the strictures in this subset of patients.[8] Larger and prospective randomized data with standardized therapeutic approaches are clearly needed to draw any definite conclusions on these regards.

Previous reports have also demonstrated that patients with esophageal atresia-EoE are at increased risk of late strictures (ie, >1 year old), and the authors speculated that the presence of early strictures are more likely to be related to ischemic complications associated with the surgical intervention per se, rather than being secondary to the presence of EoE.[8] However, in this case series the age at diagnosis and the timing of strictures did not differ among all the considered groups. Moreover, in our case series, we replicated the previous reported results showing that the response to therapy and remission rate at histopathologic examination did not differ in this group, being similar to that observed in isolated EoE. Overall, these results show that all patients with esophageal atresia should undergo extensive upper GI evaluation after surgery, supporting the most recent joint recommendations

by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology and Nutrition societies, which state that routine endoscopy and esophageal biopsies should be performed in all children with esophageal atresia at established intervals, particularly if symptoms are present.[32] We also provide evidence that the history of atopy and presence of peripheral eosinophilia are all significant risk factors for having concomitant EoE in patients with esophageal atresia and that the presence of any of these characteristics at baseline should be carefully considered and alert the clinicians to perform earlier timely investigations. Furthermore, we provide evidence that pH-impedance measures are significantly associated with presence of EoE in the esophageal atresia/trachea-esophageal fistula group.

Traditionally, these patients with esophageal atresia have been treated and followed up in surgical settings. The increasingly successful surgical techniques have contributed to the low overall mortality and the positive short-term surgical outcomes for these patients, profoundly impacting on the natural history of this disease.[3-6] Therefore, it is not uncommon for these patients to be followed up by pediatric surgeons rather than being referred to pediatric gastroenterologists, even in the presence of refractory upper GI symptoms. Our results underline the importance of an early referral to pediatric gastroenterologists, specifically in case of presence of strictures and/or refractory symptoms. In our population, 25% of the overall population had already undergone antireflux surgery at baseline and all the patients with EoE who had fundoplication in this study were only subsequently diagnosed as having EoE.

From a symptomatic perspective, patients with esophageal atresia were clinically undistinguishable from patients with esophageal atresia-EoE and esophageal atresia with esophageal eosinophilia not meeting the criteria for EoE. In particular, the latter group, which likely reflects the group with concomitant GERD, did not have any distinctive clinical characteristic compared with the EoE group, highlighting the increased risk of patients with esophageal atresia/patients with EoE being misdiagnosed as having refractory GERD. Further supporting this evidence, none of the pH-impedance measures, including AET, were associated with an increased risk of strictures, pinpointing the fact that anastomotic strictures are not secondary to reflux disease in most cases.

Our study is not without limitations. First, this is a retrospective study containing the well-known limits of this type of methodology. However, different strategies have been used to increase the consistency of our data and minimize the limitations, such as a structured form a priori generated to collect the data, and an interobserver agreement on conflicting data. Second, our results might be secondary to a population bias because all these patients were enrolled in tertiary referral centers and represented a selected population of patients undergoing motility investigations. Finally, the sample size and potential skewing of the data might be the source of a type II error. However, we do believe that the current sample size is large enough to provide clinically relevant results, although an increasing patient number would have been of value to strengthen the results.

In summary, our study provides evidence that in patients with esophageal atresia, a history of atopy and the presence of peripheral eosinophilia are predictive factors for the development of EoE, which in turn is a predictive factor for stricture occurrence. This finding strongly supports the most recent recommendations that all children should undergo routine upper GI endoscopy before fundoplication procedure and in the presence of refractory symptoms or strictures. Furthermore, in children with esophageal atresia, EoE is associated with higher esophageal acid exposure time and lower baseline impedance values suggesting that the use of pH-impedance may help the clinician in decision-making about which asymptomatic patients would benefit from upper gastrointestinal endoscopy and in paving the way for more rational management. Further larger prospective studies are warranted to confirm our encouraging findings and understand whether an early diagnosis of EoE in patients with esophageal atresia may reduce the number of unnecessary diagnostic and therapeutic procedures. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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