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Esophagitis in Pediatric Esophageal Atresia: Acid May Not Always Be the Issue

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ABSTRACT

Objective: Esophagitis is highly prevalent in patients with esophageal atresia (EA). Peptic esophagitis has long been assumed to be the primary cause of esophagitis in this population, and prolonged acid suppressive medication usage is common; such treatment is of unknown benefit and carries potential risk.

Methods: To better understand the role of commonly used antireflux treatments in EA, we analyzed all patients with repaired EA who underwent endoscopy with biopsies at our institution between January 2016 and August 2018. Macroscopic erosive and histologic esophagitis on biopsy was graded per predefined criteria. Clinical characteristics including acid suppressive medication usage, type of EA and repair, presence of hiatal hernia, and history of fundoplication were reviewed.

Results: There were 310 unique patients (33.5% long gap EA) who underwent 576 endoscopies with biopsies during the study period. Median age at endoscopy was 3.7 years (interquartile range 21–78 months). Erosive esophagitis was found in 8.7% of patients (6.1% of endoscopies); any degree of histologic eosinophilia ($\geq$1 eosinophil/high power field [HPF]) was seen in 56.8% of patients (48.8% of endoscopies), with $>$15 eosinophils/HPF seen in 15.2% of patients (12.3% of endoscopies). Acid suppression was common; 86.9% of endoscopies were preceded by acid suppressive medication use. Fundoplication had been performed in 78 patients (25.2%). Proton pump inhibitor (PPI) and/or H2 receptor antagonist (H2RA) use were the only significant predictors of reduced odds for abnormal esophageal biopsy ($P = 0.011$ for PPI, $P = 0.048$ for H2RA, and $P = 0.001$ for PPI combined with H2RA therapy). However, change in intensity of acid suppressive therapy by either dosage or frequency was not significantly associated with change in macroscopic erosive or histologic esophagitis ($P > 0.437$ and $P > 0.13$, respectively). Presence or integrity of a fundoplication was not significantly associated with esophagitis ($P = 0.236$).

Conclusions: In EA patients, acid suppressive medication therapy is associated with reduced odds of abnormal esophageal biopsy, though histologic esophagitis is highly prevalent even with high rates of acid suppressive medication use. Esophagitis is likely multifactorial in EA patients, with peptic esophagitis as only one of multiple possible etiologies for esophageal inflammation. The clinical significance of histologic eosinophilia in this population warrants further investigation.

Key Words: acid suppression therapy, esophageal atresia, esophagitis, fundoplication, proton pump inhibitor

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What Is Known

- Esophagitis is highly prevalent in patients with esophageal atresia, even years after repair.
- Acid suppressive medications are commonly prescribed to treat esophagitis, though data to support this practice is lacking.

What Is New

- Acid suppressive medical therapy appears to statistically reduce the odds of an abnormal esophageal biopsy regardless of medication class (proton pump inhibitor vs H2 receptor antagonist vs proton pump inhibitor/ H2 receptor antagonist combination).
- Despite widespread use of acid suppressive medication in our cohort, esophagitis remained highly prevalent.
- Changes in acid suppressive therapy were not significantly associated with change in erosive or histologic esophagitis.
- Clinical factors including gap length and fundoplication presence and integrity did not appear to be associated with erosive or histologic esophagitis.
- Barrett's esophagus may be seen even in very young patients taking chronic acid suppressive medication.

Esophageal atresia (EA) is one of the most common congenital gastrointestinal anomalies, affecting approximately 1 in 3500 births (1). Esophagitis is frequently encountered in patients with repaired EA; estimates of prevalence of esophagitis in in this population range from 25% to 90% (2,3). Esophagitis in this population is often attributed to gastroesophageal reflux and managed with acid suppressive medications or antireflux surgery, though as discussed in recent ESPGHAN-NASPGHAN guidelines, evidence supporting these practices is lacking (4). Although some

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EA patients have true peptic esophagitis related to gastroesophageal reflux disease, others are increasingly recognized to have alternative reasons for esophagitis, such as eosinophilic esophagitis (EoE) (5). Some patients undergo fundoplication for presumed reflux and still have moderate-to-severe esophagitis postoperatively (6). Uncontrolled esophagitis may place patients at risk for long-term complications, such as stricture and Barrett's esophagus.

In this retrospective study, we aim to understand the clinical predictors and effectiveness of antireflux treatment strategies for esophagitis in the pediatric EA population. We present the outcomes of acid suppressive medication usage and antireflux surgery in a cohort of 310 repaired EA patients who underwent endoscopy with biopsies at our tertiary referral center between 2016 and 2018, with primary outcome measures of macroscopic erosive and histologic esophagitis.

METHODS

Medical Records

This study was approved by an institutional review board. We retrospectively reviewed the electronic medical records of 310 unique patients with EA (excluding H type or isolated tracheoesophageal fistula) treated by our tertiary care referral center who underwent at least 1 upper endoscopy with biopsies between January 2016 and August 2018 (Table 1). Patient data including relevant endoscopic and surgical reports, pathology reports, clinic notes, and acid suppressive medication usage were collected by review of the medical record and caregiver interview. All upper endoscopies were performed by 1 of 2 pediatric gastroenterologists using either an Olympus XP-190 or Olympus GIF-H190 at the discretion of the endoscopist, and with the appropriate sized Radial Jaw 4 biopsy forceps (Boston Scientific Corporation, Natick, MA).

TABLE 1. Demographics of cohort, N = 310 patients

Clinical data	Median (IQR) or n (%)
Age at first endoscopy during study period (months)	40 (16–79)
Age at any endoscopy during study period (months)	44 (21–78)
Male sex	152 (49%)
Type of EA	
LGEA (regardless of type)	104 (33.5%)
Type A	2 (0.6%)
Type B	1 (0.3%)
Type C	174 (56.1%)
Type D	2 (0.6%)
Unknown	27 (8.7%)
Type of EA repair	
Esophageal anastomosis	283 (91.3%)
Gastric pullup	3 (1%)
Jejunal interposition	21 (6.8%)
Colonic interposition	3 (1%)
Gastrostomy tube present at any point during study period	159 (51.3%)
History of fundoplication ever	76 (24.5%)
Fundoplication present at any point during study period	70 (22.9%)

Clinical characteristics of our EA cohort. Long-gap esophageal atresia (LGEA) was defined by the surgeon at time of EA repair. History of fundoplication ever refers to patients who had ever undergone a fundoplication surgery. As some patients underwent interval jejunal or colonic interposition, and thus their fundoplication was taken down, patients with fundoplication present during the study period are differentiated from the larger group of fundoplications. EA = esophageal atresia; IQR = interquartile range.

All endoscopies with at least 1 biopsy during the study period were included for analysis.

Esophagitis

Evidence of erosive macroscopic esophagitis was retrospectively collected from written descriptions in endoscopy reports generated by the endoscopist at time of endoscopy.

Histologic grading of chronic esophagitis is standardized according to the number of eosinophils per high-powered field (HPF) at our institution; histologic chronic esophagitis is grouped into categories of 1 to 15 eosinophils/HPF and >15 eosinophils/HPF. Our institution has defined these cutoffs from expert consensus guidelines (7). Acute neutrophilic esophagitis (which may be seen with acute insults, such as fungal or viral infection, or with ulceration) in the absence of macroscopic erosive disease was not considered as evidence of chronic esophagitis, though was also recorded for analysis. Fungal esophagitis was identified via endoscopic visual inspection combined with esophageal brushings for culture and/or fungal forms visualized on histology. Barrett esophagus was defined as presence of histologic intestinal metaplasia on an esophageal biopsy.

Acid Suppressive Medication

Dosage and compliance with acid suppressive medications, defined as any proton pump inhibitor (PPI) and/or histamine H2-receptor antagonist (H2RA), were assessed during caregiver interviews in follow-up calls after endoscopy at the time of disclosure of biopsy results to families and recorded in the medical record. There is precedent in the *Helicobacter pylori* literature that doses of PPIs are not equivalent and must be adapted to medication type (8). Dosing equivalents are based on standard recommended dosing per pharmaceutical manufacturer's instructions. Doses of PPI were expressed as omeprazole equivalents in milligrams (mg) per kilgogram (kg) of body weight. Doses of H2RA were expressed as ranitidine equivalents in mg/kg of body weight. Equivalent doses of PPIs were defined as follows: 1 mg omeprazole equals 1 mg esomeprazole, 1 mg pantoprazole, and 1.33 mg lansoprazole. Equivalent doses of H2RAs were defined as follows: 1 mg ranitidine equals 7.5 mg famotidine. For patients with a biopsy showing >15 eosinsinophils/HPF, responsiveness to acid suppressive medication was defined as an acid suppressive medication intervention followed by repeat endoscopy with biopsies showing ≤15 eosinophils/HPF.

With respect to acid suppressive medication, increased therapy was defined as either increasing total daily dosage of a current medication or adding a second class of acid suppressive medication. Decreased therapy was defined as de-escalation of acid suppression regimen, either by discontinuation of medication(s) or decrease in total daily dosage or frequency of an existing acid suppressive medication. Medication ''responders'' had improvement on subsequent biopsy following the respective exposure such that ≤15 eosinophils/HPF was found on subsequent biopsy. Patients who were already on high doses of PPI and H2RA at the time of biopsy detecting >15 eosinophils/HPF, or who received high-dose PPI/H2RA therapy and subsequently had biopsies with persistent counts >15 eosinophils/HPF, were considered PPI/H2RA nonresponders. Patients on high-dose PPI therapy who added H2RA and then had improved histologic esophagitis on subsequent biopsy were considered PPI nonresponders who responded with addition of H2RA (''PPI plus H2RA responders''). PPI responders include patients on suboptimal dosing of PPI (<1.5 mg/kg/day of omeprazole equivalents) who subsequently had improved histology with optimization of PPI dosing, or who were previously on no PPI therapy and responded with introduction of PPI therapy.

Statistics

Continuous data on demographics and medication use are presented as medians and interquartile ranges (IQR), and categorical data are presented as frequencies and percentages. The nonparametric Wilcoxon rank sum test was used to compare continuous data between EA groups, and Fisher exact test was used to compare categorical data between esophagitis and therapy change regimens. Univariate and multivariable analysis of risk factors for abnormal biopsy was performed using generalized estimating equations (GEE) modeling with a logit link function to obtain odds ratios, 95% confidence intervals, and Wald *P* values for the risk of abnormal biopsy corresponding to each risk factor. GEE modeling was used in order to incorporate the correlation between multiple observations within the same patient into the analysis. The nonparametric Spearman rank correlation was implemented to assess the relationship between omeprazole dose, ranitidine dose, and eosinophil count.

An alpha level of 0.05 was used to determine statistical significance; however, in the analysis of change in esophagitis by initial biopsy result category, a Bonferroni-adjusted alpha level of 0.017 (0.05/3) was implemented to reduce the risk of Type I error (false-positive results) because of multiple statistical comparisons. All statistical analyses were performed using Stata version 15.0 (StataCorp, College Station, TX).

RESULTS

Clinical Characteristics

There were 310 unique patients who underwent a total of 576 endoscopies (Table 1). There were 104 patients (33.5%) with history of long-gap esophageal atresia (LGEA). Median age at any endoscopy during the study period was 44 months (IQR: 21–78 months). The median number of endoscopies per patient during the study period was 2 (IQR: 1–2); a total of 171 unique patients had more than 1 endoscopy, with median time between endoscopies of 11 months (IQR: 6–15 months) (Supplementary Figure 1, Supplemental Digital Content, *http://links.lww.com/MPG/B629*). Of 149 patients with abnormal biopsies, 53 patients (35.5%) did not have a follow-up endoscopy during the study period.

Prevalence of Esophagitis

Rates of erosive and histologic esophagitis according to patient age and acid suppressive medication status are presented in Figure 1A and B, respectively.

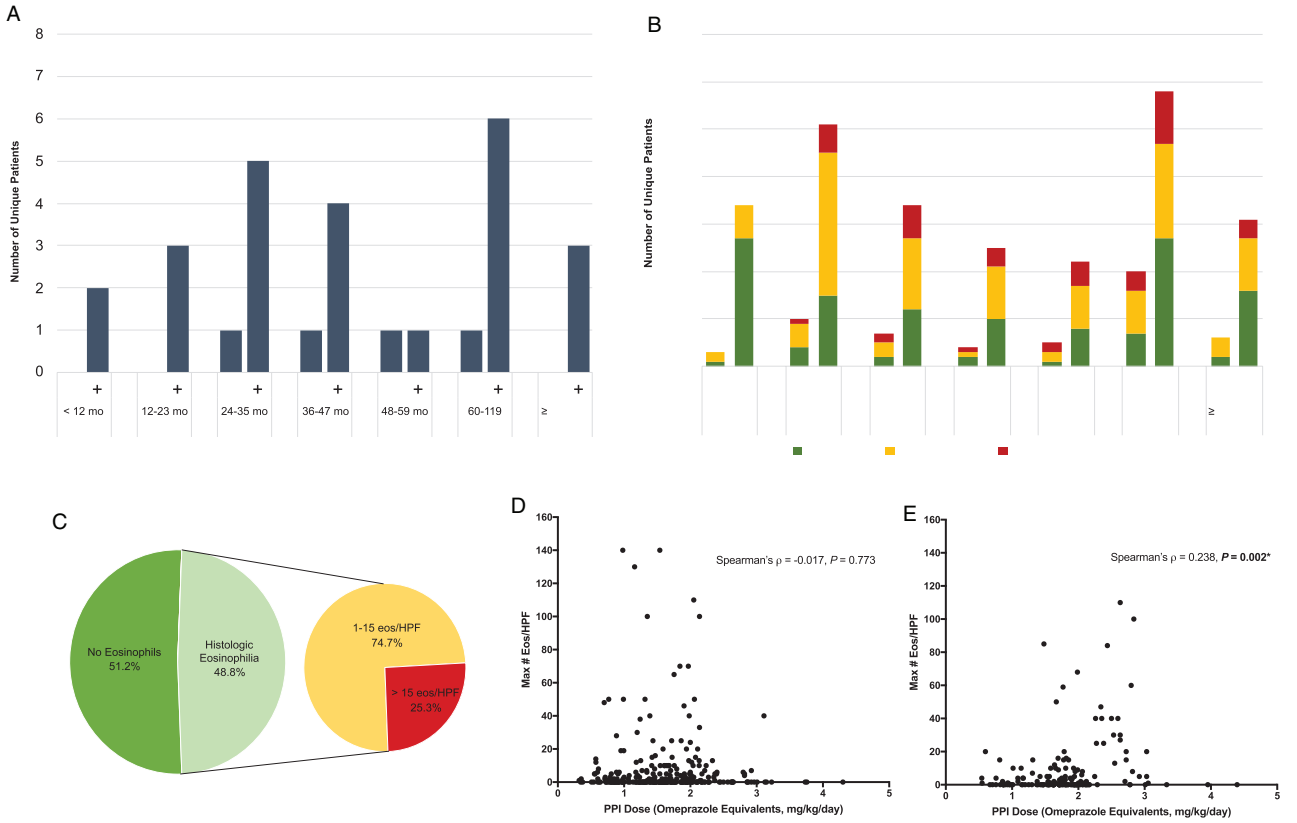

FIGURE 1. Numbers of patients with macroscopic erosive esophagitis (A) and varying degrees of histologic eosinophilia (B) by age and acid suppressive medication status, with no medications denoted by a minus sign (''−'') and any acid suppressive medication(s) denoted by a plus sign (''+''). Zero eosinophils/high powered field (HPF) are shown in green, 1 to 15 eosinophils/HPF in yellow, and >15 eosinophils/HPF in red. Three patients had Barrett esophagus (denoted by ''BE'' over the appropriate age and medication status column). (C) Prevalence of histologic esophagitis by proportion of total endoscopies. Of 576 endoscopies in our study period, 295 endoscopies (51.2%) had no eosinophils whereas 281 endoscopies (48.8%) demonstrated histologic eosinophilia. Of endoscopies with eosinophilia, most (N = 210, 74.7%) had 1 to 15 eosinophils/HPF. We found >15 eosinophils/HPF in 25.3% of endoscopies (N = 71). (D and E) Scatter plot of maximum number of eosinophils per HPF according to dose of omeprazole in patients on PPI monotherapy (D) or in patients on PPI with H2RA combination therapy (E). Spearman rank correlation was very weak for PPI monotherapy and weak for PPI with H2RA therapy. *P* values ≤0.05 are considered statistically significant and are denoted by boldface type and an asterisk (*).

Twenty-seven unique patients (8.7%) had gross erosive esophagitis seen on 35 endoscopies during the study period (Fig. 1A). Corresponding histology showed neutrophilic esophagitis in 20 endoscopies, with no eosinophils in 4 endoscopies, 1–15 eosinophils/HPF in 14 endoscopies, and >15 eosinophils/HPF in 17 endoscopies.

The prevalence of histologic eosinophilia ≥1 eosinophil/HPF was 48.8% (281/576) of all endoscopies seen in 56.8% (176/310) of unique patients (Fig. 1B and C). Seventy-one endoscopies in 47 unique patients had >15 eosinophils/HPF. Two endoscopies in 2 unique patients detected new diagnoses of Barrett esophagus with intestinal metaplasia during the study period; in addition, 1 patient in the cohort had a prior endoscopy with intestinal metaplasia on biopsy before the study period but had no intestinal metaplasia on their study period biopsy (Fig. 1B). Barrett esophagus was diagnosed at a median age 71 months (range 64–174 months). Two patients with Barrett esophagus had nonlong gap type C EA and 1 patient had LGEA. The prevalence of acute neutrophilic esophagitis was 16.3% of endoscopies (94/576) in 20.6% of unique patients (64/310) and was most commonly seen with fungal esophagitis or macroscopic erosive disease.

Acid Suppressive Medication Use

In 574 endoscopies, acid suppressive medication usage both before and after the endoscopy were documented in the medical record. Patients were taking acid suppression medications at most endoscopies (N = 499 endoscopies; 86.9%). Patients with history of LGEA were significantly more likely to be treated with more aggressive classes of acid suppressive therapy (PPI or PPI with H2RA, $P < 0.001$, Supplementary Figure 2, Supplemental Digital Content, *http://links.lww.com/MPG/B629*). Dosing within medication class was generally similar across patients regardless of EA gap length, though patients with LGEA received significantly lower doses of H2RA whenever given as the sole acid suppressive therapy (Supplementary Table 1a and 1b, Supplemental Digital Content, *http://links.lww.com/MPG/B629*).

Of 63 patients on no PPI therapy (no acid suppressive therapy [N = 44] or on H2RA monotherapy [N = 19]), 46 patients had 1 to 15 eosinophils/HPF and 17 patients had >15 eosinophils/HPF. For patients on PPI, increasing dose of PPI was very weakly correlated with decreasing eosinophil count by Spearman rank correlation for patients on PPI monotherapy, though this finding was not statistically significant ($\rho = -0.017$, $P = 0.773$, Fig. 1D and E). Increasing dose of PPI was weakly but significantly correlated with increasing eosinophil count for patients on PPI with H2RA therapy ($\rho = 0.238$, $P = 0.002$).

Univariate analysis using GEE to account for multiple measurements of the same patient over time identified only acid suppressive medication therapy (either H2RA, PPI, or both) as significantly associated with reduced odds for abnormal biopsy (Table 2). Age at endoscopy, gap length, anastomosis type, fundoplication, and hiatal hernia were not significantly associated with abnormal biopsy. To adjust for multiple potentially interrelated predictor variables, a multivariate GEE model still identified only acid suppressive medication therapy as statistically significantly associated with reduced odds of abnormal biopsy (Table 3). No clinical predictors were found to be significantly associated with odds of erosive esophagitis by univariate or multivariate analysis, likely because of low numbers of endoscopies with erosive disease (Tables 4 and 5).

Effect of Acid Suppressive Medication Intervention on Esophagitis

Out of the 35 endoscopies with gross erosive esophagitis, 20 endoscopies had subsequent repeat endoscopy after a known acid suppressive medication intervention. Erosive esophagitis resolved in 8 patients who increased therapy, in 3 patients who had no change in therapy, and in 1 patient who decreased therapy. Out of the 8 patients already on combination high-dose PPI and H2RA, 5 patients had persistent erosive disease on subsequent endoscopy. By Fisher exact test, there was a trend towards change in erosive

TABLE 2. Univariate analysis of risk factors for abnormal biopsy

Variable	Normal (N = 295)	Abnormal (N = 281)	*P* value
Medications			
None	30 (10%)	45 (16%)	**0.019***
PPI only	150 (51%)	136 (49%)	
H2RA only	30 (10%)	19 (7%)	
PPI and H2RA	84 (29%)	80 (29%)	
EA group			
LGEA	104 (35%)	112 (40%)	0.111
Non-LGEA	173 (59%)	141 (50%)	
Unknown	18 (6%)	28 (10%)	
Anastomosis type			
Esophageal	268 (91%)	267 (95%)	0.275
Jejunal interposition	17 (6%)	12 (4%)	
Colonic interposition	4 (1%)	0 (0%)	
Gastric pullup/tube	6 (2%)	2 (1%)	
Fundoplication	77 (26%)	92 (33%)	0.082
Hiatal hernia			
No hernia	115 (65%)	95 (55%)	0.069
Hernia <2 cm	23 (13%)	42 (24%)	
Hernia ≥2 cm	39 (22%)	35 (20%)	
Age at biopsy (months)	43 (19–76)	45 (24–80)	0.585

Univariate model generated to identify predictors of an abnormal biopsy, defined as ≥1 eosinophil per high powered field. Values are frequency (percent) for categorical data and median (interquartile range) for continuous data. This model utilized generalized estimating equations (GEE) to account for multiple endoscopies/measurements within the same patient. EA = esophageal atresia; LGEA = long-gap esophageal atresia; PPI = proton pump inhibitor; H2RA = H2 receptor antagonist. *P* values ≤ 0.05 are considered statistically significant and are denoted by bold face type and an asterisk (*).

TABLE 3. Multivariate generalized estimating equation model for abnormal biopsy

Variable	Odds ratio	95% confidence interval	*P* value
Medications			
None	Reference	.	.
PPI only	0.51	(0.3–0.86)	**0.011***
H2RA only	0.48	(0.23–0.99)	**0.048***
PPI and H2RA	0.37	(0.2–0.67)	**0.001***
EA group			
LGEA	1.34	(0.86–2.08)	0.203
Non-LGEA	Reference	.	
Unknown	1.79	(0.84–3.81)	0.129
Fundoplication	1.44	(0.92–2.27)	0.113
Age at biopsy	1	(1–1)	0.809

Multivariate model using GEE identifying predictors of an abnormal biopsy. *P* values ≤ 0.05 are considered statistically significant and are denoted by bold face type and an asterisk (*). EA = esophageal atresia; GEE = generalized estimating equations; LGEA = long-gap esophageal atresia; PPI = proton pump inhibitor; H2RA = H2 receptor antagonist.

TABLE 4. Univariate analysis of risk factors for erosive esophagitis

Variable	Normal (n = 541)	Erosive (n = 35)	*P* value
Medications			
None	70 (13%)	4 (11%)	0.619
PPI only	274 (51%)	12 (34%)	
H2RA only	47 (9%)	2 (6%)	
PPI and H2RA	147 (27%)	17 (49%)	
EA group			
LGEA	198 (37%)	17 (49%)	0.487
Non-LGEA	299 (55%)	15 (43%)	
Unknown	43 (8%)	3 (9%)	
Anastomosis type			
Esophageal	501 (93%)	34 (97%)	0.489
Jejunal interposition	29 (5%)	0 (0%)	
Colonic interposition	4 (1%)	0 (0%)	
Gastric pullup/tube	6 (1%)	1 (3%)	
Fundoplication	166 (31%)	10 (29%)	0.453
Hiatal hernia			
No hernia	201 (62%)	9 (35%)	0.238
Hernia <2 cm	59 (18%)	6 (23%)	
Hernia ≥2 cm	62 (19%)	11 (42%)	
Age at biopsy (months)	43 (21–78)	51 (33–80)	0.234

Univariate model using GEE generated to identify predictors of erosive esophagitis. EA = esophageal atresia; LGEA = long-gap esophageal atresia; PPI = proton pump inhibitor; H2RA = H2 receptor antagonist.

esophagitis with change in acid suppressive medication therapy that did not achieve statistical significance ($P = 0.059$).

A total of 137 endoscopies with any degree of histologic eosinophilia had subsequent repeat endoscopy and biopsy after a known medication intervention. Despite the finding that acid suppression use was significantly associated with reduced odds of abnormal biopsy by multivariate GEE model, change in acid suppressive therapy was not significantly associated with change in histologic esophagitis on subsequent endoscopies (Table 6).

TABLE 5. Multivariate generalized estimating equation model for erosive esophagitis

Variable	Odds Ratio	95% confidence interval	*P* value
Medications			
None	Reference	.	.
PPI only	0.64	(0.2–1.99)	0.437
H2RA only	0.77	(0.15–4.07)	0.759
PPI and H2RA	1.21	(0.37–3.92)	0.755
EA group			
LGEA	1.79	(0.72–4.44)	0.207
sNon-LGEA	Reference	.	
Unknown	1.31	(0.28–6.11)	0.729
Fundoplication	0.63	(0.24–1.67)	0.355
Age at biopsy (months)	1	(1–1.01)	0.200

Multivariate model using GEE identifying predictors of erosive esophagitis. EA = esophageal atresia; GEE = generalized estimating equations; LGEA = long-gap esophageal atresia; PPI = proton pump inhibitor; H2RA = H2 receptor antagonist.

Histologic Esophagitis With Greater Than 15 Eosinophils/High Power Field

We further examined the subgroup of patients who met histologic criteria of >15 eosinophils/HPF. During the study period, 47 unique patients (15.2%) had at least 1 biopsy with >15 eosinsinophils/HPF. These 47 patients underwent a total of 124 endoscopies; 71 of these 124 endoscopies had >15 eosinophils/HPF, and the remaining 53 endoscopies had ≤15 eosinophils/HPF. The distribution of histologic eosinophilia exceeding 15 eosinophils/HPF was proximal only (9/71 endoscopies), distal only (51/71 endoscopies), or both proximal and distal (11/71 endoscopies).

Of the 47 unique patients found to have at least 1 biopsy with >15 eosinophils/HPF, follow-up data from repeat endoscopy was available for 31 patients. Of these 31 patients, 10 patients were PPI responders, 6 patients failed to respond to PPI but responded with addition of H2RA to their PPI, and 15 patients were PPI with H2RA nonresponders (Supplementary Figure 4, Supplemental Digital Content, *http://links.lww.com/MPG/B629*). Within the group of PPI with H2RA nonresponders, 6 patients were medically treated for eosinophilic esophagitis (EoE) with swallowed viscous corticosteroid (N = 5) or dietary elimination (N = 1). Of note, these 6 patients had supporting clinical factors, such as family history or coexistence of atopic disorders. Of the remaining 9 acid suppression nonresponders, 1 patient subsequently experienced improved histology with addition of erythromycin for gastric dysmotility and 3 patients experienced apparent spontaneous improvement with no identifiable medication or surgical intervention in between biopsies (of note, spontaneous improvement may have been related to sampling error as histologic eosinophilia may be patchy). The remaining 5 patients remain on high-dose acid suppression and are undergoing further diagnostic evaluation (e.g. allergy testing, impedance testing).

Fundoplication

Nissen fundoplication is by far the most common antireflux surgery performed by our institution. Fundoplication had ever been performed in 78 patients (25.2%). Six patients with a history of prior fundoplication had subsequently undergone jejunal or colonic interposition before the start of the study period, leaving 72 patients with fundoplications in situ during the study period. Of these 72 patients, 26 patients had fundoplication during the study period, and 46 patients had pre-existing fundoplications before the start of the study period.

A total of 125 endoscopies with biopsies described the appearance of the fundoplication wrap in 72 patients. Most had an intact wrap seen on endoscopy (Table 7). Degree of histologic esophagitis was not significantly associated with presence of or integrity of a fundoplication wrap ($P = 0.236$). Macroscopic erosive esophagitis was not significantly associated with fundoplication by univariate GEE model ($P = 0.453$) or multivariate GEE model ($P = 0.355$), likely because of small numbers of patients with erosive esophagitis.

Twenty-six patients underwent fundoplication during the study period, most often for symptoms of reflux such as vomiting (N = 22 patients) and/or esophageal stricture suspected to be related to reflux (N = 7); 14 of 26 patients who underwent fundoplication during the study period had endoscopy with biopsies both before and after their fundoplication procedure. Of patients whose acid suppressive medications were kept constant between these endoscopies (N = 11), 8 had no change in histologic esophagitis (N = 2 patients with normal histology, N = 4 patients with 1–15 eosinophils/HPF, and N = 2 patients with >15 eosinophils/HPF), 2 patients had worsening esophagitis (N = 1 from normal to 1–15 eosinophils/HPF, and

TABLE 6. Repeat endoscopy after medication change for histologic esophagitis, N = 137 EGD pairs

	Increase therapy	No change	Decrease therapy		*P* value
				a	0.139
Esophagitis not improved	23 (46%)	48 (59%)	2 (33%)	b	0.682
Esophagitis improved	27 (54%)	33 (41%)	4 (67%)	c	0.395

A total of 137 endoscopies with any degree of histologic esophagitis had subsequent repeat endoscopy and biopsy after a known medication intervention (either increased therapy, no change in therapy, or decreased therapy). Patients were categorized as esophagitis ''not improved'' (no change or worsening esophagitis) or ''improved'' (improved esophagitis) compared with esophagitis severity detected at initial endoscopy as defined in the Methods section. *P* values were obtained using the Chi-square test or Fisher exact test as appropriate. For *P* values, a = increased therapy vs. no change, b = increased therapy vs. decreased therapy, and c = no change vs. decreased therapy. Statistical significance occurs at Bonferroni-adjusted $P < 0.017$.

N = 1 from 1–15 to >15 eosinophils/HPF), and 1 patient had improved esophagitis (from 1–15 eosinophils/HPF to normal). Only 2 patients who underwent fundoplication during the study period had erosive esophagitis; 1 patient had resolution of erosions following fundoplication, and 1 patient had resolution of erosions following intensification of acid suppressive medication regimen before fundoplication being performed.

DISCUSSION

We found that esophagitis in patients with repaired EA is prevalent despite our widespread use of acid suppressive medication. With evolving concerns around risks of chronic PPI use, such as possible increased susceptibility to gastrointestinal or respiratory infections and micronutrient deficiencies, better understanding of the utility of acid suppression in EA patients is critical (9).

Here we present the largest pediatric study to date of esophagitis in EA and commonly employed antireflux strategies. To our knowledge, this study is the first report of longitudinal findings with changes in acid suppressive medication in pediatric EA patients. Our study is limited as a retrospective study of a single tertiary referral center with a cohort that is potentially biased towards increased complexity or refractory cases, as well as by lack of pH-impedance data, lack of dietary and feeding route histories, and incomplete follow-up data. In addition, our pathologists do not routinely report features, such as papillary elongation or basal cell hyperplasia in clinical pathology reports; whereas these features would have helped to provide a more complete picture of histologic esophagitis, these features are not routinely reported by our pathology group because they depend heavily on esophageal specimen orientation (10–12) and have been described to have lower interobserver reproducibility than eosinophil count, neutrophil count, and erosions (64–74% vs 83–97%) (13), Despite these limitations, this study provides the first in-depth evaluation of antacid strategies in a large cohort of over 300 pediatric EA patients.

In this study, acid suppressive medication use was not associated with erosive esophagitis, though low numbers of patients with erosive disease limit our power to detect such a relationship. Acid suppression was the only significant factor associated with reduced odds of abnormal esophageal biopsy. However, despite widespread acid suppressive medication use in this cohort, approximately half of these patients still had histologic esophagitis, highlighting the importance of surveillance endoscopy even in patients on acid suppression. Increasing dose of PPI very weakly trended towards lower eosinophil counts in patients on monotherapy, though this finding did not reach statistical significance; conversely, increasing PPI dose in patients on PPI with H2RA was weakly and significantly correlated with increasing eosinophils/HPF, likely because of a tendency to use more aggressive acid suppression in patients with more severe esophagitis. Interestingly, we did not find evidence to support that changes in acid suppressive medication were significantly associated with change in histologic esophagitis in individual patients, though there was a trend towards association between change in acid suppressive therapy with change in macroscopic erosive esophagitis. Although our study could be underpowered to identify a small effect of varied acid suppressive therapy intensity, it is also possible that acid suppression response is binary, with dose adjustments or addition of secondary agents not likely to produce improvements in patients who initially fail to respond. Further study of factors that might predict acid suppression nonresponse in esophagitis of EA patients is needed.

We found that fundoplication presence or integrity was not significantly associated with change in esophagitis. Although our study is likely underpowered to detect changes in esophagitis before and after fundoplication because of small numbers of patients who underwent fundoplication during the study period, we found that most patients (72.7%; 8/11) had no change in esophagitis before and after fundoplication when acid suppressive medications were held constant. Our findings differ from another recent study, which showed a reduction in esophagitis prevalence from 65% to 29% in 193 patients with pre- and post-fundoplication endoscopies; however, this study does not report concurrent antacid medication usage and instead notes that medication decisions were made on an individualized basis (14). The same group later found a trend towards post-fundoplication esophagitis improvement in a group of 11 patients with moderate or severe esophagitis who were all on either PPI or H2RA; after fundoplication, 8 children had no esophagitis, 2 had mild esophagitis, and 1had severe esophagitis (6). Further prospective study of the effect of fundoplication on esophagitis is needed.

We were particularly interested to investigate our population of EA patients with >15 eosinophils/HPF. According to the most recent EoE guidelines, diagnostic criteria for EoE require:

TABLE 7. Histologic esophagitis and fundoplication endoscopic appearance

	Intact wrap (N = 88 EGDs)	Partial wrap (N = 25 EGDs)	Unwrapped (N = 12 EGDs)	Never had fundoplication (N = 410 EGDs)
Normal	44 (50%)	11 (44%)	4 (33%)	219 (53%)
1–15 Eosinophils/HPF	38 (43%)	9 (36%)	6 (50%)	140 (34%)
>15 Eosinophils/HPF	6 (7%)	5 (20%)	2 (33%)	51 (12%)

By Fisher exact test ($P = 0.236$), the presence and integrity of Nissen fundoplication wrap as assessed visually by endoscopy was not significantly associated with esophagitis. EGD = endoscopy; HPF = high-powered field.

symptoms of esophageal dysfunction, eosinophil-predominant inflammation on esophageal biopsy (classically >15 eosinophils/HPF), and exclusion of other potential responsible causes for symptoms and biopsy findings (15). Application of these criteria to EA patients is problematic, as many patients experience symptoms of esophageal dysfunction related to abnormal esophageal development and postsurgical sequelae, it is often impossible to exclude these factors as contributors to symptomatology, and many may meet the eosinophil/HPF cutoff with alternative reasons for esophagitis, such as reflux (15). In our cohort, 15.2% of patients met the EoE cutoff of >15 eosinophils/HPF (similar to a previously reported prevalence of 17% of patients in another EA cohort in a study of EoE in EA) (5), but only 6 cases were treated for EoE during the study period. One limiting factor in estimating the prevalence of EoE in our cohort is our high usage rates of PPI, which is now considered a therapeutic option for EoE (15). Although our study is also limited by incomplete follow-up data, some patients who met the >15 eosinophil/HPF criterion responded to non-EoE-directed interventions to maximize reflux treatment, such as addition of H2RA therapy (N = 6) or addition of gastric motility medication (N = 1). In addition, 3 patients improved with no dietary or medical intervention (N = 3), though it is possible their eosinophilia was missed because of the patchy nature of histology. Taken all together, this data suggests that use of eosinophil count alone in EA patients to diagnose EoE as previously reported is likely insufficient (5). All cases where treatment of EoE was initiated involved reliance on other clinical factors, such as gross endoscopic findings consistent with EoE (eg, furrowing or circular rings) or by suggestive history, such as positive allergy testing, coexistence of other atopic disorders, or family history. Our study highlights the critical need for adapted criteria for EoE diagnosis in the EA population to better identify candidates for EoE-directed therapies.

Patients with EA are estimated to be at 4-fold higher risk for the precancerous condition of Barrett esophagus than the general population (2,4,16). We observed Barrett esophagus in 3 patients in our very young cohort (1.0%, 3/310 patients), demonstrating that Barrett esophagus may occur even in very young patients. Our youngest patient with Barrett esophagus was 5.3 years old. Barrett esophagus was seen in these patients despite all 3 patients receiving longstanding acid suppressive therapy (2 patients on PPI with H2RA and 1 on PPI), raising the intriguing possibility of longstanding, nonpeptic inflammation contributing to the development of Barrett esophagus in this population. Surveillance endoscopy is crucial to identifying these young patients with Barrett esophagus so that appropriate monitoring may be implemented before the onset of dysplasia.

Beyond gastroesophageal reflux disease and EoE, there are likely other mechanisms unique to EA patients that contribute to esophagitis. Esophageal motility is near universally disturbed in EA patients; manometry and impedance studies in patients with EA have found abnormal patterns of peristalsis and bolus transit in 80% to 100% of patients (2,17–20). It has been posited that patients with EA may develop esophageal inflammation related to stasis of food and saliva in the esophagus (21). Though studies of esophageal motility and esophagitis in EA are lacking, 1 retrospective study of 101 patients found that low esophageal distal wave amplitudes and nonpropagating peristalsis were strong predictive factors of Barrett esophagus in an EA cohort (2). Stasis of material, whether it be swallowed food and saliva or refluxed acid or bile, offers 1 plausible mechanism of esophageal inflammation in this group. Further study towards understanding the mechanisms by which esophagitis occurs in EA is crucial to identifying rational and effective treatment strategies.

Our study highlights the great importance of endoscopic surveillance in pediatric EA patients. Even though our data showed that acid suppressive medication use was the only significant factor associated with reduced odds of abnormal esophageal biopsy, nearly half of patients in our cohort had evidence of histologic eosinophilia, and 16% of all endoscopies revealed major findings including erosive disease, histologic eosinophilia exceeding 15 eosinophils/HPF, or intestinal metaplasia. The clinical relevance of microscopic esophagitis in the absence of erosive esophageal disease is controversial (22–24), and the implications of microscopic esophagitis for outcomes in EA have never been studied. Nevertheless, chronic esophageal inflammation has been shown to lead to increased risk for complications, such as Barrett esophagus and esophageal adenocarcinoma (25,26). Peptic esophagitis can lead to stricture, and untreated EoE (which most often lacks erosive macroscopic features) progresses from an inflammatory phenotype to fibrostenosis in most patients (27). Study of long-term outcomes in EA patients with isolated microscopic esophagitis is needed. Although our study was not powered to identify an optimal endoscopic screening interval, the high prevalence of actionable findings, such as esophagitis, fungal infection, and Barrett esophagus suggest that current endoscopic surveillance guidelines of 3 endoscopies throughout childhood may lead to delayed recognition and treatment of these conditions (4). Further prospective study of optimal endoscopic interval is needed.

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