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Surveillance Endoscopy in Pediatric Esophageal Atresia: Toward an Evidence-Based Algorithm

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Brief title: Surveillance in Pediatric Esophageal Atresia

Abstract

Background: Individuals with esophageal atresia (EA) have lifelong increased risk for mucosal and structural pathology of the esophagus. The utility of surveillance endoscopy to detect clinically meaningful pathology has been underexplored in pediatric EA. We hypothesized that surveillance endoscopy in pediatric EA has high clinical yield, even in the absence of symptoms.

Methods: The medical records of all EA patients who underwent at least one surveillance endoscopy between March 2004 and March 2023 at an international EA referral center were retrospectively reviewed. The primary outcome was endoscopic identification of pathology leading to an escalation in medical, endoscopic, or surgical management. Logistic regression analysis examined predictors of actionable findings. Nelson-Aalen analysis estimated optimal endoscopic surveillance intervals.

Results: Five hundred forty-six children with EA underwent 1473 surveillance endoscopies spanning 3687 person-years of follow up time. A total of 770 endoscopies (52.2%) in 394 unique patients (72.2%) had actionable pathology. Esophagitis leading to escalation of therapy was the most frequently encountered finding (N = 484 endoscopies, 32.9%), with most esophagitis attributed to acid reflux. Barrett's esophagus (intestinal metaplasia) was identified in 7 unique patients (1.3%) at a median age of 11.3 years. No dysplastic lesions were identified. Actionable findings leading to surgical intervention were found in 55 children (N=30 refractory reflux, N=25 tracheoesophageal fistulas). Significant predictors of actionable pathology included increasing age, long gap atresia, and hiatal hernia. Symptoms were not predictive of actionable findings, except dysphagia, which was associated with stricture. Nelson-Aalen analysis predicted occurrence of an actionable finding every 5 years.

Conclusions: Surveillance endoscopy uncovers high rates of actionable pathology even in asymptomatic children with EA. Based on the findings of the current study, a pediatric EA surveillance endoscopy algorithm is proposed.

Key Words: esophageal atresia, endoscopy, surveillance, screening, esophagitis

Abbreviations: EA, esophageal atresia; EoE, eosinophilic esophagitis; TEF, tracheoesophageal fistula; EPF, esophagopulmonary fistula; PPI, proton pump inhibitor; H2RA, histamine 2 receptor antagonist; IQR, interquartile range; EGD, esophagogastroduodenoscopy; ESCC, esophageal squamous cell carcinoma; EGID, eosinophilic gastrointestinal disease.

Introduction

Individuals with repaired esophageal atresia (EA) are at increased risk of gastrointestinal pathology including esophagitis, Barrett's esophagus, and esophageal cancers.(1) Structural pathology such as stricture or recurrence of tracheoesophageal fistula (TEF) can develop at any age.(2–4) Neither chronic acid suppression nor fundoplication is sufficient to eliminate the risk of esophagitis or stricture,(5, 6) and patients with significant pathology are frequently asymptomatic.(7–12) Endoscopic surveillance for these issues is therefore recommended by expert consensus guidelines to identify, treat, and prevent these long-term complications.(13) However, evidence supporting the practice is sparse and the optimal time intervals for endoscopic surveillance are not defined. We hypothesized surveillance endoscopy will have actionable findings in at least 20% of patients (based on minimum rates of esophagitis previously reported(13)), and that endoscopy is indicated more frequently than current guidelines to avoid delayed detection of actionable early pathology.

Methods

This study was institutional review board approved. Surveillance EA endoscopies performed at our international referral center from March 2004 to March 2023 were retrospectively reviewed. Our typical surveillance protocol involves annual gastroenterology clinic visits and an initial esophagogastroduodenoscopy (EGD) around age 12-18 months, with recommended annual clinic visits and ongoing surveillance endoscopies every 1-5 years throughout childhood, taking into account any factors deemed high risk for pathology. Generally, patients with higher perceived risk for actionable pathology were advised to return for repeat surveillance endoscopy on shorter time intervals (e.g. 1 year), while patients with multiple normal prior endoscopies were advised to return for surveillance on longer time intervals (e.g. 5 years). Other factors that played a role in surveillance timeline included desire to combine surveillance with unrelated sedated

procedures (such that surveillance endoscopy timeline was adjusted to align with the planned anesthetic to minimize additional anesthetics). Surveillance endoscopies at our institution involve 2-3 levels of esophageal biopsies even when the mucosa appears visually normal. Our surveillance endoscopies also may involve an intra-endoscopy contrast esophagram to assess overall esophageal contour, especially to define evolving diverticulae that may become problematically enlarged from repetitive food trapping, delineate a hiatal hernia when present, and assess for recurrent or missed TEF.(4) Endoscopies performed within the first 6 months of esophageal surgery, for follow up or treatment of a previously identified issue (e.g. reassessment of esophagitis after changing therapy) within the prior 6 months, or part of planned therapeutic series to endoscopically treat known stricture were excluded. Symptom data were abstracted from clinical documentation; dysphagia was defined as food impactions, subjective feelings of food sticking, and/or reliance on behavior modifications such as drinking liquids to push food down or limiting the diet to age-inappropriate but tolerable textures. Reflux included heartburn, regurgitation, vomiting, belching, sour breath, and/or throat clearing. Poor weight gain was defined as downward crossing of 2 or more centile lines between successive clinical follow ups. Actionable endoscopic findings were defined as any finding which prompted a change in management, including erosive (e.g. Los Angeles classification grades A-D) and non-erosive esophagitis (any combination of gross congestion, furrowing, erythema, etc. that led to an escalation in medical treatment), or significant histologic esophagitis (> 15 eosinophils/high powered field) that prompted escalation of therapy; eosinophilic esophagitis (EoE); Barrett's esophagus (intestinal metaplasia); stricture requiring endoscopic or surgical therapy; and/or TEF or esophagopulmonary fistula (EPF).

We define hiatal hernia as at least 1cm of gastric folds present above the level of diaphragmatic pinch on endoscopy. Findings that are generally considered to be benign were excluded: gastric fundic gland polyps while on proton pump inhibitor (PPI), pancreatic rests, gastric inlet patches of the proximal esophagus, lymphoid aggregates, and submucosal lipomas.

Escalation of therapy was defined as addition of new medication(s), dosage or frequency intensification, escalating therapy class (e.g. switching from histamine 2 receptor antagonist (H2RA) to PPI), endoscopic therapy (e.g. stricture dilation), or surgery (e.g. TEF repair).

Statistical Analysis

Continuous data are presented as medians and interquartile ranges (IQR). Categorical data are presented as frequencies and percentages. Univariate comparisons were done using the Wilcoxon rank sum test for continuous data and Fisher's exact test for categorical data. Univariate and multivariable logistic regression analyses were implemented to identify independent predictors of actionable endoscopic findings. Variables with $P<0.05$ upon univariate analysis were included in multivariable modeling. Regression analysis results are presented as adjusted odds ratios, 95% confidence intervals (CI) and P values. To analyze repeated events, a modulated renewal framework was implement using the Nelson-Aalen cumulative hazard estimator. Cumulative hazard functions are plotted with corresponding 95% confidence intervals to estimate the cumulative risk of an event up to a given time. A $P<0.05$ was considered as statistically significant. Statistical analyses were performed using Stata (version 17.0, StataCorp LLC, College Station, Texas).

Results

Of 704 patients with EA seen at our center, a total of 546 unique patients underwent 1473 surveillance endoscopies spanning 3687 person-years of follow up time (Table 1; SDC 1, http://links.lww.com/JACS/A329). Each patient underwent a median 2 surveillance endoscopies

(interquartile range (IQR) 1-4 endoscopies) with median total follow up time per patient of 5.3 years (IQR 2.8-9 years). A majority had type C EA (N=390 patients, 71%). Most endoscopies were performed on acid suppression (SDC 2, http://links.lww.com/JACS/A329; N=1121, 76%). Fifty-eight patients were noted to have undergone their last surveillance endoscopy five or more years prior to the end of the study period, suggesting loss to surveillance follow up. Historical surgical characteristics are summarized in SDC 3. http://links.lww.com/JACS/A329.

A total of 770 surveillance endoscopies (52%) in 394 unique patients (72%) had at least one actionable finding (Figures 1 and 2; Table 2). Of these, 518 endoscopies had mucosal pathology and 409 had structural pathology, with a significant proportion having both mucosal and structural pathology (Figure 1). The fraction of endoscopies with actionable findings tended to increase with increasing age (Figure 2). The vast majority of identified pathology was esophageal (N=744 endoscopies, 97%).

Esophagitis leading to therapy escalation was the most frequently encountered finding (N=484 endoscopies, 32.9%), with most esophagitis attributed to acid reflux. Barrett's esophagus (intestinal metaplasia) was identified in 11 endoscopies (0.7%) in 7 unique patients (1.3%) at a median age of 11.3 years (IQR 6.9-25 years); all but one of these endoscopies was performed on acid suppression. No dysplastic lesions were identified. Of endoscopies with grossly normal mucosa in the esophagus (N=893), 86 (9.6%) uncovered significant histologic esophagitis with at least one biopsy exceeding 15 eosinophils per high powered field. Thirty-five unique patients (6.4%) were diagnosed with eosinophilic esophagitis.

Actionable extra-esophageal pathology included low rates of celiac disease, Crohn's disease, eosinophilic gastroenteritis, *H. pylori* gastritis, and nonspecific gastritis and duodenitis (Table 2). Stricture prompting endoscopic intervention, most commonly dilation, was present in 386 endoscopies (26%, SDC 4, http://links.lww.com/JACS/A329). Strictures were most commonly

anastomotic (N=302). Other narrowings included tight fundoplication wraps (N=53), congenital esophageal strictures (N=25), peptic strictures (N=11), and eosinophilic esophagitis stricture (N=1), with 21 patients having more than one type of narrowing treated within a single endoscopy. Symptoms frequently informed decisions to perform a therapeutic intervention, with dysphagia or other feeding difficulties preceding 310 endoscopies (80%) where a stricture was identified.

Twenty-eight endoscopies (1.9%) identified TEF or EPF, of which 25 were treated surgically and 3 endoscopically. Six endoscopies occurring at a median 4 years post-surgery discovered complications at retained surgical material including 2 *Actinomyces* esophageal suture abscesses, 1 mixed flora esophageal suture abscess, an eroding pledget in the esophageal wall, an eroding piece of Silastic™ in the esophageal wall, and an eroding bovine pericardial patch used to augment a fundoplication wrap.

In 1473 endoscopies, 8 (0.5%) were associated with complications. Five patients experienced adverse events likely related to anesthesia or coincident non-EGD procedure(s), including 4 patients with aspiration pneumonitis or pneumonia requiring hospitalization (of which 3 had also undergone coincident bronchoscopy at the time of endoscopy), and 1 patient who experienced a venous air embolism requiring an ICU hospitalization. Three patients who underwent endoscopic therapeutic maneuvers for stricture experienced complications: 1 esophageal leak after endoscopic incisional therapy (EIT) successfully managed with stent placement; 1 with no definitive esophageal leak but thin walled appearance of esophagus who was admitted for overnight observation without further complication; and 1 with esophageal leak following dilation who was hospitalized and successfully managed with an esophageal wound vacuum sponge (EVAC).

Predictors of Actionable Findings

Demographic characteristics that were significantly associated with actionable endoscopic findings in univariate analyses included increasing age (OR 1.03, $p = 0.001$) and long gap EA (OR 1.57, $p < 0.001$) (Table 3).

Acid suppression was associated with significantly reduced odds of actionable finding (OR 0.78, $p = 0.048$). History of fundoplication was not protective but rather was associated with greater odds of actionable finding (OR 1.52, $p < 0.001$). Hiatal hernia was significantly associated with actionable findings (OR 1.72, $p < 0.001$).

All predictors identified by univariate analyses were found by multivariable logistic regression analysis to retain their statistical significance, except fundoplication (Table 4).

Predictive Value of an Initially Normal Endoscopy

In the 381 children who had more than one surveillance endoscopy in the cohort, 187 had a normal first endoscopy and 194 had an abnormal first endoscopy. By logistic regression analysis adjusting for age (as older patients had more opportunities for surveillance), the odds of ever having a future abnormal endoscopy given a normal first endoscopy were 0.392 (95% CI 0.247, 0.624; $p < 0.001$).

Predictive Value of Symptoms

Bothersome gastrointestinal symptoms (occurring at least weekly) of reflux, dysphagia, other feeding difficulties, and/or abdominal pain were present preceding 515 (35%) endoscopies. The only symptom significantly associated with actionable finding was dysphagia (Table 3; odds ratio (OR) 5.80, 95% confidence interval (CI) (4.067, 8.272); $p < 0.001$). Excluding treated stricture as an actionable finding eliminated the statistical significance of dysphagia (OR 1.17, 95% CI (0.878, 1.546), $p = 0.29$). No other symptom was identified to be significantly related to actionable finding outcome.

Additional subgroup analysis was performed for asymptomatic children (N=953, 65%, Table 2). Prevalences of actionable findings were generally not significantly different between the asymptomatic and symptomatic subgroups with few exceptions: stricture was associated with dysphagia, as already noted; children with fistulas were more likely to be symptomatic (p = 0.008); and symptomatic children with nonerosive esophagitis were more likely to be treated with gastric accommodation- and motility-directed therapies such as cyproheptadine, erythromycin, metoclopramide, and/or prucalopride. Otherwise there were no statistically significant differences in endoscopic pathology between the asymptomatic and symptomatic subgroups.

Occurrence of Actionable Findings throughout Childhood

The Nelson-Aalen cumulative hazard function was calculated to investigate the expected number of occurrences of actionable findings per patient over time (Figure 3). Per patient, occurrence of an actionable finding was predicted approximately every 5 years.

De-Escalation of Therapy

Acid suppression was reduced or discontinued after 310 reassuring endoscopies in 233 unique patients. Therapy was subsequently re-escalated after development of esophagitis off acid suppression in 59 endoscopies (19%) in 57 unique patients.

There were a total of 313 endoscopies (in 232 unique patients) performed off acid suppression entirely, with no consistent nor any PRN acid suppressive medication use leading up to the endoscopy. Of these, only 143 endoscopies (46%) in 112 unique patients remained off acid suppressive therapy following the endoscopy due to presence of actionable reflux injury findings.

Discussion

The ESPGHAN-NASGPHAN consensus guidelines for pediatric EA management have advocated for 3 endoscopies throughout childhood: 1 after stopping PPI therapy, 1 before age 10 years, and 1 at transition to adulthood, though these recommendations are derived from expert opinion and outcomes of smaller studies.(11, 13–21) The present study identified high rates of actionable pathology in this large retrospective study of over 500 children with EA, and supports the practice of surveillance endoscopy in the pediatric EA population. Nearly three-quarters of subjects had at least one actionable endoscopy over the course of their follow up. Of note, even very young children with EA had high rates of pathology in our study, with over 40% of 1 year olds found to have actionable endoscopic findings. Moreover, over half of the endoscopies performed on acid suppression had actionable pathology, highlighting that children on acid suppression should not necessarily be assumed to be low risk for endoscopic pathology, contrasting with current consensus recommendations.

Importantly, symptoms were generally not predictive of endoscopic findings in our study; indeed, symptoms have been repeatedly shown to be unreliable markers of pathology in EA.(22–25) The only symptom found to be significantly associated with actionable findings was dysphagia; however, in this retrospective analysis, this association is likely driven by the endoscopist's prior symptom knowledge influencing the decision to dilate, thereby rendering the endoscopy finding "actionable" by default. We therefore feel symptoms should prompt investigation, but lack of symptoms does not obviate the need for vigilant endoscopic surveillance in pediatric EA.

The goal of pediatric surveillance endoscopy is timely detection of early precursor pathology, such as uncontrolled esophagitis, and to intervene to prevent long-term complications such as dysplasia. Several adult surveillance protocols have been proposed given higher rates of pre-

malignant and malignant lesions in EA compared to the general population.(26, 27) Barrett's esophagus is 4-5 times more common in adult EA and 26 times more common in pediatric EA compared to the general population.(26, 28–31) Esophageal cancers are more prevalent in EA and appear to strike at younger ages; prevalence of esophageal squamous carcinoma have been estimated as high as 50-100 fold higher than the general population(1, 32) and have been found in EA patients as young as 36 years old. Esophageal adenocarcinomas, thought to arise from Barrett's esophagus, have afflicted EA patients as young as 20 years old.(33)

One adult screening protocol has therefore advocated to begin surveillance starting at 20 years, as their youngest patient with a "clinically relevant premalignant lesion" (Barrett's esophagus) was 20.9 years old; however, their practice specifically excludes pediatric patients from surveillance due to need for general anesthesia.(26) We and others have demonstrated that patients with EA may develop Barrett's esophagus at much younger ages: as young as 5.3 years old in our cohort (median age 11.3 years) and as young as 2 years old in others.(21) The youngest reported child (non-EA) in the literature to have Barrett's esophagus complicated by an esophageal adenocarcinoma was 10 years old.(34) If following a strategy guided by this criterion of using the earliest detected Barrett's lesion to determine screening onset, endoscopic surveillance should begin much sooner in childhood than has been previously proposed.(26, 27, 35)

Our practice stratifies patients based on risk for actionable findings and adjusts surveillance intervals accordingly (Figure 4). We typically perform an initial surveillance endoscopy around age 12-18 months of age. To maximize the information yield from the initial endoscopy, a patient may first wean off acid suppression approximately 3 months before endoscopy to permit evaluation for both anatomy and esophagitis off acid suppression. Subsequent surveillance is performed according to our algorithm and/or within at most 6-12 months of any acid suppression

changes. We consider history of intestinal metaplasia to be an absolute contraindication to acid suppression discontinuation. In our practice, relative contraindications to weaning acid suppression include prior erosive esophagitis, prior failed acid suppression discontinuation attempt(s) with rebound esophagitis, or hiatal hernia; if acid suppression is weaned in these high risk situations, we feel close follow up endoscopy is warranted to assess for rebound pathology. As previously described, acid suppression was associated with significantly reduced odds of actionable finding, (6) but this has little clinical consequence when it comes to surveillance: 51% of acid-suppressed endoscopies had actionable endoscopic findings (SDC 5, http://links.lww.com/JACS/A329). Thus, we argue acid suppression does not obviate the need for surveillance. In addition, biopsies unearthed significant histologic esophagitis even when the mucosa was deemed grossly normal, confirming the importance of biopsies during surveillance regardless of tissue appearance. Importantly, not all esophagitis exceeding 15 eosinophils per high powered field should be automatically diagnosed as eosinophilic esophagitis, as this degree of histologic eosinophilia may also be frequently seen with reflux injury.(6, 36)

Both pH-impedance testing and endoscopy after stopping PPI are recommended by the ESPGHAN-NASPGHAN guidelines in order to safely de-escalate acid suppression.(13) Our practice for acid suppression de-escalation typically involves endoscopy alone. There are no consensus “normal” values for pH-impedance reflux parameters in either healthy or EA children,(37, 38) and pH-impedance has failed to show any predictive correlation with actual esophagitis in multiple pediatric studies.(39–41) In particular, EA children with “normal” numbers of reflux events may not adequately clear their refluxate in the context of poor esophageal motility and may still develop reflux injury. Moreover, pH-impedance tracings in EA require manual review by an experienced reader, with automated analysis being highly unreliable in the setting of low baseline impedance values.(42) Given these challenges with abstracting any

predictive data from pH-impedance in EA, as well as the psychosocial, financial, and physical burdens placed by this invasive type of 24-hour testing, our practice is to empirically de-escalate acid suppression in children without contraindications to doing so when there is no gross esophagitis and biopsies show no or minimal inflammation (generally less than 5 eosinophils per high powered field). This empiric de-escalation is followed by repeat endoscopy within at most 6-12 months to assess for rebound esophagitis (Figure 4). Within our cohort who underwent acid suppression de-escalation, rebound esophagitis that required therapy re-escalation was observed in nearly 20% of cases, confirming the importance of repeat endoscopy after acid suppression changes.

When encountered, symptomatic strictures should be treated.(43–46) Symptoms may include classic dysphagia but may also present more subtly such as poor weight gain, with patients not recognizing or verbalizing overt dysphagia.(47, 48) For asymptomatic children found to have a narrowing (20% of identified strictures in the current study), we consider empiric dilation in cases where the child has not yet reached an International Dysphagia Diet Standardization Initiative level 7 regular diet; for example, empiric dilation may be reasonable for a stricture that does not comfortably permit slim (5-6mm diameter) endoscope passage in an asymptomatic infant who takes only liquids and purees, as even tight strictures may accommodate these textures but are likely to become problematic with increasing complexity of the diet. In deciding to dilate, we loosely follow age-based diameter guidelines that we have described elsewhere, taking into account any symptoms and the esophageal contour (aiming for smooth transitions between proximal esophagus, anastomosis, and distal esophagus without significant lumenal scar intrusion or diverticulum formation, as chronic or repetitive subclinical impactions in such diverticulae may anecdotally result in deep esophageal pockets that can later become

symptomatic and difficult to non-surgically manage) (SDC 6, http://links.lww.com/JACS/A329).(25, 44)

We propose our pediatric surveillance intervals based on the Nelson-Aalen cumulative hazard analysis of our large pediatric dataset in which the cumulative hazard reaches 1 roughly every 5 years; thus, every 5 years, a child is expected to have an actionable finding. Children with an initial normal endoscopy had significantly reduced odds of future abnormal endoscopies and may represent a lower risk subgroup; additional prospective study is needed to confirm this observation. For patients at higher risk for actionable findings (e.g. with risk factors identified in our logistic regression analyses, including long gap atresia and hiatal hernia; or prior high risk pathology such as Barrett's esophagus, erosive esophagitis, and/or rebound esophagitis), we conservatively shorten the surveillance interval to 2-3 years since the cumulative risk of actionable finding is approximately 0.5 after that period.

A limitation of any pediatric EA surveillance program is the incomplete understanding of pathogenesis of pre-malignant and malignant lesions in EA. It is unclear if the factors that increase risk of Barrett's esophagus and esophageal cancer are modifiable risk factors. Though acid reflux injury is a risk factor for Barrett's esophagus,(49) biopsy confirmed intestinal metaplasia of the esophagus was observed in 7 patients in this study, 6 of whom had been on acid suppression prior to Barrett's detection. Esophageal squamous cell carcinoma (ESCC) is more common in EA for unknown reasons; some groups have hypothesized that its pathogenesis may be similar to that in achalasia, where stasis and dysmotility expose the esophageal epithelium to bacterial overgrowth, resulting in chronic inflammation and subsequent dysplasia.(50, 51) In these cases it is unknown if chronic acid suppression further distorts the esophageal microbiome and what the long-term effect of that distortion may be. Cases of ESCC in EA tend to be located at or near the surgical anastomosis,(27, 32, 52) raising the possibility

that factors associated with the anastomosis itself (e.g. chronic inflammation at foreign body sutures), dilation procedures, and/or use of cytotoxic agents such as mitomycin C to treat stricture may contribute to repetitive inflammatory insults that in turn increase the risk of ESCC.(32, 50)

Limitations to this study include its retrospective design with a potentially biased population of motivated families who chose to travel to our referral center for care. Our cases skew towards long gap EA (with 24.1% long gap in our cohort compared to a 10% expected prevalence of long gap in EA overall). While our center's practice has always been to perform surveillance endoscopies in children with EA, there was no pre-prescribed protocol followed during the study period. However, the same 4 gastroenterologists with sub-specialization in EA perform our surveillance, and within this subgroup there has been a general agreement and consistency in surveillance practice over time as described in our methods. We present endoscopic data in all children who underwent endoscopies as part of their long-term follow up, though some children reported symptoms at the time of their annual follow up, rendering their scopes arguably not purely "surveillance" in nature; however, subgroup analysis in the asymptomatic cohort (comprising the majority of studied cases) generally mirrored the findings in the larger cohort, with high rates of endoscopically identified pathology (429/958, 45%). Notably, the findings from the inclusion of symptomatic children in the current study support the conclusions from multiple previous reports which have identified a lack of correlation between symptoms and pathology.(7–12)

Additionally, while intestinal metaplasia is generally agreed to carry risk of malignant transformation, there is controversy around the significance of gastric metaplasia;(31, 53, 54) in this retrospective study we are unable to reliably define rates of gastric metaplasia versus

sampling of the Z-line, though we acknowledge some practitioners would consider gastric metaplasia a potentially actionable finding for which we do not account in the current study.

In addition, there are limitations to consider specifically due to lack of pulmonary symptom data in the current study. For example, anecdotally we have observed that interposition conduits subjectively appear to become dilated and tortuous over time, and may be associated with respiratory morbidity that are not captured in this purely gastrointestinal symptom dataset. In a similar vein, fistulas were identified more frequently in the symptomatic group in the current study, though because fistulas may present solely with pulmonary symptoms, children flagged as "asymptomatic" in this study may in fact not have been truly be asymptomatic. Future multidisciplinary collaborative efforts in studying esophageal atresia outcomes are needed and ongoing.(55)

Despite these limitations, the current study is bolstered by large patient numbers and is the largest study of surveillance to date in pediatric EA(14). The current study is bolstered by inclusion of a broader array of early actionable findings than has been previously investigated, with the vast majority of prior work focusing on the outcome of Barrett's esophagus.(11, 13–21) We identified high clinical yield of surveillance endoscopy, and based on cumulative hazard analysis we propose a pediatric surveillance endoscopy algorithm with defined time interval recommendations. Future studies should explore the psychosocial burden posed by repeated endoscopies in childhood, weigh potential neurocognitive risks of anesthetics in children against the clinical benefits of maintaining a healthy functional esophagus, and financial cost-benefit analysis on a population level. Ongoing prospective efforts across multiple centers will help refine optimal surveillance practices.(55)

Conclusions

Surveillance endoscopy uncovers high rates of actionable pathology even in asymptomatic children with EA. Based on the findings of the current study, the first evidence-supported pediatric EA surveillance endoscopy algorithm is proposed.

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Contributors Statement Page

Dr. Jessica Yasuda conceptualized and designed the study, designed the data collection instruments, collected data, coordinated and supervised data collection, carried out statistical analyses, drafted the initial manuscript, and critically reviewed and revised the manuscript.

Dr. Ali Kamran, Dr. Maximiliano Servin-Rojas, and Mr. Cameron Hayes designed the data collection instruments, collected data, and critically reviewed and revised the manuscript.

Mr. Steven Staffa designed the study, carried out statistical analyses, and critically reviewed and revised the manuscript.

Drs. Peter Ngo, Denis Chang, Thomas Hamilton, Somala Mohammed, Farokh Demehri, and Benjamin Zendejas critically reviewed and revised the manuscript.

Dr. Michael Manfredi conceptualized and designed the study, and critically reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Figure Legend

Figure 1. Numbers and categories of actionable findings detected on surveillance endoscopies.

Figure 2. Proportions of all endoscopies with and without actionable findings stratified by age (bar), with overlying percentage of endoscopies with any actionable finding trended over time.

Figure 3. Nelson-Aalen cumulative hazard curve demonstrating accumulated risk for occurrence of actionable endoscopic findings over time.

Figure 4. Proposed pediatric surveillance endoscopy algorithm, based on (A) presence or (B) absence of actionable pathology at index endoscopy. Any surveillance esophagogastroduodenoscopy (EGD) should at minimum include 2-3 levels of esophageal biopsies and carefully examine the distal esophagus / gastroesophageal junction to identify areas suspicious for Barret's esophagus and to document the presence of a hiatal hernia, which is a risk factor for future actionable pathology. Barrett's esophagus is proposed to be an absolute contraindication to acid suppression wean; relative contraindications to weaning acid suppression include prior erosive esophagitis, prior failed acid suppression discontinuation attempt(s) with rebound esophagitis, or hiatal hernia; if acid suppression is weaned in these high-risk situations, we feel close follow up endoscopy is warranted to assess for rebound pathology.

Precis

Surveillance endoscopy, even in asymptomatic children on acid suppressive therapy, has high diagnostic yield in pediatric esophageal atresia.

Table 1. Demographic Characteristics (N = 546 Unique Patients)

Variable	Data
Male sex, n (%)	298 (54.6)
Age at first surveillance EGD, y, median (IQR)	2.3 (1.3, 4.7)
No. of surveillance EGDs per patient, median (IQR)	2 (1, 4)
Time between surveillance EGDs per patient, y, median (IQR)	1.3 (0.9, 2)
Total follow-up time per patient, y, median (IQR)	5.3 (2.8–9.0)
Type of EA, n (%)	
A	92 (16.8)
B	40 (7.3)
C	390 (71.4)
D	11 (2)
H	5 (0.9)
Unknown	8 (1.5)
VACTERL association, n (%)	
Vertebral anomaly	191 (35.0)
Anorectal malformation	63 (11.5)
Cardiovascular anomaly	219 (40.1)
Renal anomaly	136 (24.9)
Limb anomaly	57 (10.4)
Other congenital anomalies and genetic disorders, n (%)	
Congenital esophageal stenosis	31 (5.7)
Duodenal atresia	30 (5.5)
Trisomy 21	21 (3.8)
CHARGE syndrome	9 (1.6)

EA types are defined by the anatomic configuration of the upper and lower esophageal pouches and the tracheoesophageal fistula (if present) as described by Gross in 1953.(56)

EA, esophageal atresia; EGD, esophagogastroduodenoscopy

Table 2. Prevalence of Actionable Findings per Endoscopy

Variable	Full cohort, N (%)	Asymptomatic subgroup, N = 958 (65%)	Symptomatic subgroup, N = 515 (35%)	p Value
Inflammatory esophageal pathology				
Erosive esophagitis	151 (10.3)	88 (9.2)	63 (12.2)	0.0725
Non-erosive gross esophagitis prompting therapy				
Acid reflux therapy escalated	155 (10.5)	107 (11.2)	48 (9.3)	0.2858
EoE therapy escalated	52 (3.5)	27 (2.8)	25 (4.9)	0.054
Motility therapy escalated	31 (2.1)	14 (1.5)	17 (3.3)	0.023*
Antifungal therapy escalated	64 (4.3)	36 (3.8)	28 (5.4)	0.1424
Significant histologic esophagitis† with grossly normal mucosa	86 (5.8)	57 (6.0)	29 (5.6)	0.817
Barrett's esophagus	11 (0.7)	7 (0.7)	4 (0.8)	0.999
Hyperplastic polyp of esophagus (foveolar)	3 (0.2)	2 (0.2)	1 (0.2)	0.999
Anatomic esophageal pathology				
Stricture or narrowing treated with endoscopic therapy	386 (26.2)	179 (18.8)	207 (40.2)	<0.001*
TEF/EPF	28 (1.9)	11 (1.2)	17 (3.3)	0.008*
Abscess at retained/eroded surgical material (eg suture, pledget, silastic)	5 (0.3)	5 (0.5)	0 (0)	0.1691
Extra-esophageal pathology				
Celiac disease	3 (0.2)	1 (0.1)	2 (0.4)	0.2827
Crohn’s disease	2 (0.1)	1 (0.1)	1 (0.2)	0.999
EGID of stomach and/or duodenum	2 (0.1)	1 (0.1)	1 (0.2)	0.999
Actionable gastric polyp/mass	5 (0.3)	2 (0.2)	3 (0.6)	0.351
H pylori	4 (0.3)	3 (0.3)	1 (0.2)	0.999
Gross nonspecific gastritis‡	38 (2.6)	26 (2.7)	12 (2.3)	0.7323
Gross nonspecific duodenitis‡	12 (0.8)	7 (0.7)	5 (1)	0.7625

Data presented as n (%).

*Statistically significant; p values reflect outcomes of statistical comparisons between the asymptomatic and symptomatic subgroups.

†Significant histologic esophagitis was defined as greater than or equal to 15 eosinophils per high powered field on at least one esophageal biopsy specimen.

‡Gross gastritis and duodenitis is only included if the finding was associated with an escalation of therapy following the endoscopy.

EoE, eosinophilic esophagitis; EGID, eosinophilic gastrointestinal disease; EPF, esophagopulmonary fistula; TEF, tracheoesophageal fistula

Table 3. Univariate Logistic Regression Analyses of Presence vs Absence of Actionable Findings

Variable	Actionable finding (N = 769)	No actionable finding (N = 704)	Odds ratio for actionable finding	95% confidence interval	p Value
Age at endoscopy, y, median (IQR)	4.8 (2.5-8.4)	4.2 (2.2 – 7.4)	1.03	(1.014, 1.056)	0.001*
Male sex, n (%)	413 (54)	345 (49)	1.21	(0.984, 1.482)	0.071
Gap length, n (%)					
Short	412 (54)	450 (64)	Ref		
Long	354 (46)	246 (35)	1.57	(1.273, 1.940)	< 0.001*
H type	2 (0.3)	5 (0.7)	0.44	(0.084, 2.264)	0.324
Surgery type, n (%)					
Primary	701 (91)	629 (89)	Ref	.	.
Redo	68 (9)	75 (11)	0.81	(0.576, 1.149)	0.242
Conduit anatomy, n (%)					
EE	708 (92)	627 (89)	Ref	.	.
EJ roux	36 (5)	33 (5)	0.97	(0.595, 1.568)	0.889
EJG	9 (1)	21 (3)	0.38	(0.172, 0.835)	0.016*
EG	12 (2)	5 (1)	2.13	(0.745, 6.066)	0.159
EC	4 (0.5)	18 (3)	0.20	(0.066, 0.585)	0.003*
Genetic disorder (Trisomy 21, CHARGE), n (%)	60 (8)	45 (6)	1.24	(0.830, 1.850)	0.294
Duodenal atresia, n (%)	45 (6)	36 (5)	1.16	(0.741, 1.825)	0.512
Fundoplication, n (%)	235 (31)	158 (22)	1.52	(1.203, 1.922)	< 0.001*
Hiatal hernia, n (%)	204 (28)	123 (19)	1.72	(1.333, 2.216)	< 0.001*
Acid suppression therapy, n (%)	571 (75)	551 (79)	0.78	(0.610, 0.998)	0.048*
Symptom, n (%)					
Dysphagia	205 (28)	41 (6)	5.80	(4.067, 8.272)	< 0.001*
Reflux	171 (23)	130 (19)	1.25	(0.964, 1.611)	0.093

Abdominal pain	46 (6)	39 (6)	1.08	(0.693, 1.671)	0.744
Poor oral intake	37 (6)	29 (5)	1.17	(0.707, 1.919)	0.549
Poor weight gain or weight loss	81 (11)	62 (9)	1.23	(0.865, 1.735)	0.253
Any symptom	337 (44)	178 (25)	2.31	(1.847, 2.878)	< 0.001*

Conduit anatomy refers to the configuration of (neo)-esophageal conduit: native esophago-esophageal (EE) anastomosis, jejunal interposition consisting of esophago-jejunal anastomosis with Roux-en-Y gastric bypass (EJ roux), jejunal interposition with esophago-jejunal anastomosis and jejunal-gastric anastomosis (EJG), esophago-gastric anastomosis as in gastric pull up or gastric tube (EG), and colonic interposition with esophago-colonic anastomosis (EC). Redo surgeries include surgical stricture revisions or stricture resections, surgical leak repairs, surgical fistula ligations or repairs, and interposition surgeries. Symptoms were included for analysis if present on at least a weekly basis.

*Statistically significant.

Table 4. Multivariable Logistic Regression Analysis of Presence vs Absence of Actionable Findings

Variable	Odds ratio for actionable finding	95% confidence interval	p Value
Age at endoscopy, y	1.02	(1.002, 1.054)	0.032*
Gap length			
Short	Ref	-	-
Long	1.82	(1.372, 2.402)	<0.001*
H type	0.47	(0.079, 2.809)	0.409
Anastomosis type			
EE	Ref	-	-
EJ roux	0.68	(0.381, 1.199)	0.181
EJ G	0.35	(0.137, 0.873)	0.025*
EG	1.16	(0.364, 3.679)	0.805
EC	0.06	(0.017, 0.228)	<0.001*
Fundoplication	1.12	(0.836, 1.498)	0.449
Hiatal hernia	1.50	(1.104, 2.025)	0.009*
Acid suppression	0.74	(0.558, 0.986)	0.040*
Dysphagia	7.00	(4.725, 10.364)	<0.001*

*Statistically significant.

EC, colonic interposition with esophago-colonic anastomosis; EE, end-to-end; EG, esophago-gastric anastomosis as in gastric pull up or gastric tube; EJG, esophago-jejunal anastomosis and jejunal-gastric anastomosis; EJ roux, Roux-en-Y gastric bypass

Figure 1

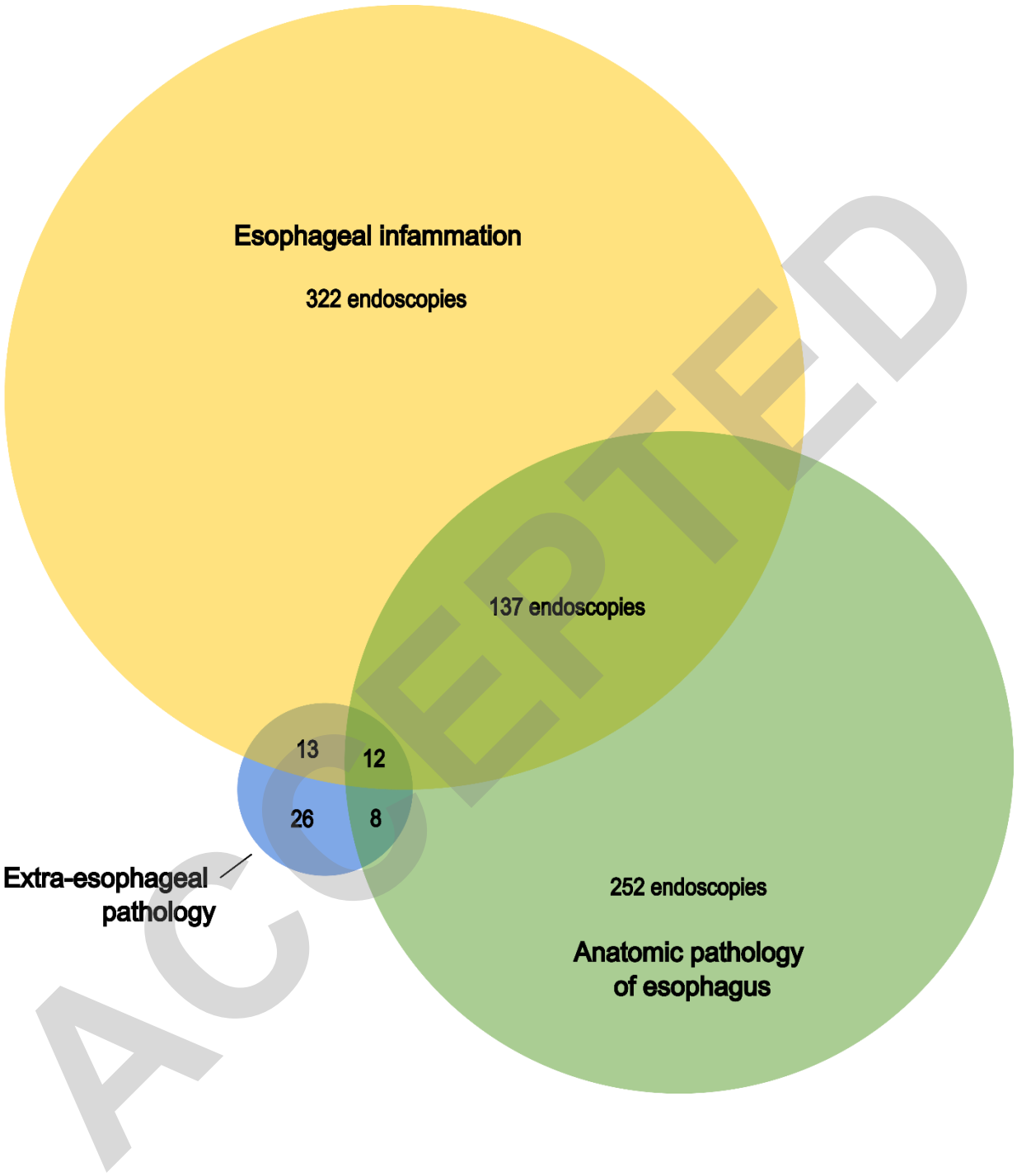

Figure 2

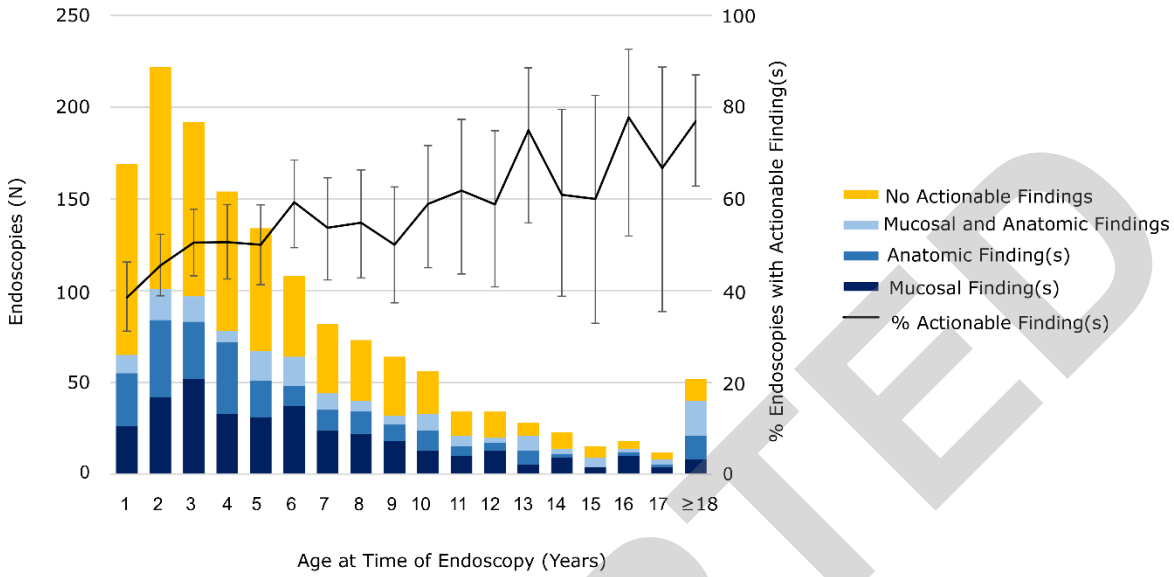

Figure 3

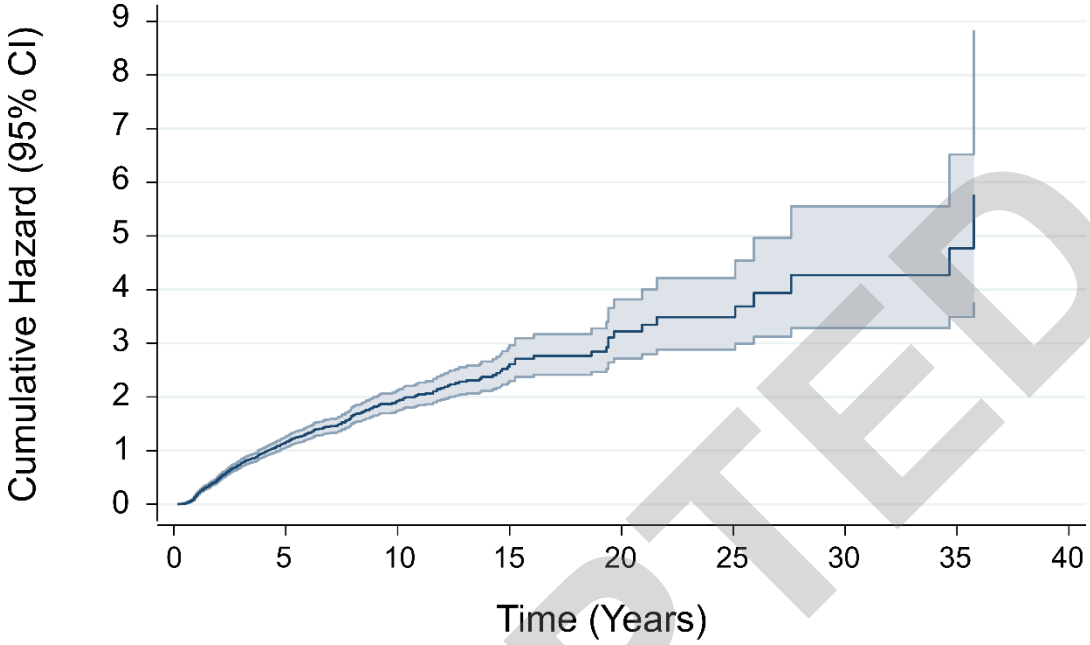

Figure 4