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"How to care for patients with EA-TEF; the known and the unknown"

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Abstract

Purpose of Review: Guidelines were recently published highlighting why esophageal atresia (EA) patients are prone to complication risks, and the need for long term follow up. In this review, we will focus on how to investigate and treat potential complications, as well as the pros and cons of different investigative and treatment modalities, and what areas continue to need further research.

Recent findings: EA patients are at high risk for gastroesophageal reflux and esophageal strictures, and the sequela that result. Extraintestinal manifestations of gastroesophageal reflux disease (GERD) can appear similar to other pathologic diagnoses commonly found in EA patients, such as congenital stricture, eosinophilic esophagitis, esophageal dysmotility, tracheomalacia, recurrent fistula, aspiration, etc. Therefore, it is important to have a standardized way to monitor for these issues. pH impedance allows for detection of nonacid reflux and the height of reflux, which are important in correlating symptoms with reflux episodes.

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Summary: A multidisciplinary approach is beneficial in evaluating and monitoring EA patients in the long term.

Keywords

Esophageal atresia; Tracheoesophageal Fistula; Review; Complications; Gastroesophageal Reflux Disease; Multichannel Intraluminal Impedance; Anastamotic Strictures; Eosinophilic Esophagitis; Long-Term Follow up

Introduction

Esophageal atresia (EA) is a congenital anomaly with an incidence ranging from 1 in 2,400 to 1 in 4,500 births worldwide.[1–4] With improvements in surgical and perioperative care, survival rates now exceed 90%.[4, 5] This increased survival prompts a need to focus on long-term complications. The most common problems patients with EA are at risk for include: gastroesophageal reflux disease (GERD) with or without esophagitis, Barrett's esophagus (BE), dysphagia, strictures, eosinophilic esophagitis, feeding and nutritional problems, recurrent respiratory tract infections, persistent cough, and wheezing. The most recently published consensus guidelines, reviewed literature and gathered experts' opinions on the epidemiology of EA and its natural history, and made recommendation on the management of gastrointestinal complications in this cohort.[6] In this article, we will review in greater detail how to investigate and treat the gastrointestinal complications associated with EA. Finally, we will focus on the long-term consequences of EA in adulthood and on the importance of the follow-up of adult patients with EA.

Gastroesophageal Reflux Disease

EA patients are at increased risk for gastroesophageal reflux due both to intrinsic dysmotility and to structural factors. They have abnormal in utero development of the myenteric plexus of the esophagus, with decreased or absent interstitial cells of Cajal.[7] This results in impaired peristalsis and lower esophageal sphincter function. In addition, there is abnormal development of the esophageal smooth muscle, with distorted smooth muscle tissue and tracheobronchial remnants found in the esophagus.[8] Structurally, EA patients, particularly those with long gap EA, can also lose some function of the anti-reflux barrier after surgical repair. In long gap atresia, gastric pull up causes the lower esophageal sphincter to no longer be overlapped by the crural diaphragm, weakens the phrenoesophageal ligament, decreases the angle of His, and creates a hiatal hernia.[9–11]

The prevalence of GERD in EA patients ranges from 20% to 63%, with the range discrepancy in published papers being due to patient selection (age, symptoms) and diagnostic methods used to define GERD. GERD can persist lifelong, but few longitudinal studies have evaluated the natural history of GERD in EA patients. It appears to be most frequent in the first 5 years of life. In a longitudinal study evaluating GERD in 61 children with EA, Koivusalo et al. found that the prevalence of GERD gradually increased from 6 months of age to 5 years of age, from 16% to 51%.[12] After age 3, it was rare to find new cases of GERD and the patients who did present with it were symptomatic.[12]

Complications that can result from chronic GERD include dysphagia, esophagitis, BE, stricture formation, silent aspiration, failure to thrive, and impaired quality of life.[13] There is a reported incidence of strictures in EA patients ranging from 18-50%, with the majority occurring within the first year of life.[14–16] Aerodigestive complications can result from GER reaching the proximal esophagus and entering the larynx. These include: cough, hoarseness, aspiration pneumonia, chronic lung disease with increased oxygen requirement, worsening tracheomalacia, airway reactivity,[11] and brief resolved unexplained events.

Treatment

Given the high incidence GERD and its complications in the EA/TEF cohort, the consensus guidelines recommend treating all EA/TEF infants with proton pump inhibitors (PPIs) during the first year of life, and continuing treatment based on reflux symptoms thereafter. [6]

While there are no randomized controlled trials regarding evaluating the efficacy of different acid suppressants in outcomes of EA, a systematic review showed that medical management of GERD via acid suppression was successful in reducing respiratory and gastrointestinal symptoms, as well as improving weight gain. [17] This was true for both PPI and histamine-2-receptor antagonists (H2RAs). There is no evidence to justify prescribing a higher dose of PPI to EA patients, as there is no evidence of EA patients having an abnormally high acid secretion or showing a resistance to PPIs. Prokinetics have not been shown to be effective in treating GERD in EA patients. While EA patients with long standing esophagitis are at increased risk for Barrett's Esophagus, which is a premalignant condition,[18] long-term PPI treatment is not generally recommended in pediatrics, given the increasing knowledge of adverse effects that can result from prolonged treatment. In addition, the utility of long term PPI use has not been studied well in EA children. Therefore, one should weigh the risks and benefits of long term PPI use in this population, and reassess the need for PPI on a regular basis.

Acid suppression to prevent strictures—Given that acid gastroesophageal reflux is a significant contributor to stricture formation, PPI therapy has been recommended for the treatment of recurrent strictures.[6] In an observational study evaluating the time frame of esophageal dilation needs, the majority of dilations (51%) occurred in the first year of life, with 16% required during the second year, and 33% during years 2-15.[19]

Although there are only a few prospective studies evaluating the use of PPI and H2RAs in preventing stricture formation, those that exist show minimal effect on prevention. In a retrospective observational study that compared infants with EA and symptomatic GERD on PPI to asymptomatic infants on prophylactic PPI for the first year of life, there was no difference noted in the median age of first anastomotic stenosis, the number of dilations until 1 year of age and 5 years of age, or the incidence of anastomotic strictures.[20] Long gap EA, high birth weight, and anastomotic tension were found to be independent risk factors for stricture formation. When comparing outcomes in EA patients receiving 3-month and 12-month PPI prophylaxis following surgical repair, there was no difference in the prevalence of anastomotic stricture or median number of dilations required in each group.[21] This was

supported by the results of another study that compared EA patients on no therapy and EA patients on 3 months of postoperative PPI prophylaxis.[22] Patients who received the shorter duration of PPI prophylaxis, however, did have an earlier need for dilation.

In a study assessing long-term efficacy of prophylactic H2RA, patients who were on and off treatment showed no difference in dilation rate within a 1 year follow up.[23] However, in the late postoperative period, those receiving H2RAs had a greater improvement in their stricture.

Fundoplication—As described above, patients with EA have an altered esophageal development and anatomy, which makes them less likely to respond to positional or dietary treatment, and can make them refractory to medical treatment.[24] Although acid suppression has shown to be beneficial, it oftentimes cannot prevent stenosis.[22] If medical management fails, fundoplication or trans-pyloric feeds should be considered. The following groups may require fundoplication due to severe GERD not well controlled on medical therapy: those with refractory anastomotic strictures, long gap EA, persistent vomiting with failure to thrive, severe esophagitis, and extraesophageal symptoms related to GERD including cyanotic spells, repeated aspiration, and recurrent pneumonia.[6, 24] Six to 60% of EA-TEF patients ultimately undergo fundoplication.[24]

Fundoplications in EA are often associated with a higher rate of complications than in non-EA patients.[25] While in most cases creating a competent anti-reflux valve via fundoplication alleviates symptoms, these effects can be transient.[24] In studies evaluating post antireflux surgery outcomes in non-EA patients, airway symptoms such as apnea, pneumonia, respiratory admissions, and asthma have been reported as decreased post-surgery,[26] though in select studies they have been noted to worsen post-surgery.[27–29] Recurrent reflux and wrap disruption can be due to the presence of an already shortened esophagus under tension. Postoperative dysphagia is also more common in EA, likely due to the dyskinetic esophagus being unable to overcome the increased LES resistance caused by the fundoplication. In a study of 21 EA-TEF patients who underwent fundoplication for GERD, wrap disruption and recurrent reflux occurred in 33%, which was a higher incidence than the 10% rate seen at the same institution in patients without EA.[30] Looking at six case series with a total of 282 patients with EA following fundoplication for GERD, wrap failure rate requiring reoperation ranged between 0-32%.[26] Given that patients with EA can have worsened esophageal clearance as a result of fundoplication, caution is recommended in proceeding with fundoplication in patients who have respiratory symptoms alone.[6]

There are no controlled trials investigating the role and outcomes of antireflux surgery in EA patients. Surgical options for antireflux surgery include open or laparascopic fundoplication, loose fundoplication, partial anterior (Thal, Ashcraft, Boix-Ochoa) or posterior (Toupet) fundoplications.[24] When comparing outcomes between partial and complete fundoplication in a group of children, some of whom had TEF, post surgery symptoms of vomiting, dysphagia, retching, and need for reoperation were not statistically different between the 2 groups, ranging from 10-40%.[31] A significantly greater proportion of patients were able to achieve long-term symptom- and medication-free recovery with the

partial fundoplication as compared to the complete fundoplication. When comparing the laparascopic and open Nissen fundoplications, the laparascopic procedure was associated with less retching and airway complications postoperatively. The two procedures were comparable in terms of wound infection, redo procedure rates, and timing to reach full feeds. [32] Though effects may be temporary, resolution of esophageal stricture can be seen after antireflux surgery.[33, 34]

It is important to note that not all patients with long gap atresia require fundoplication. In a study that followed 9 patients with long gap atresia, who had their native esophagus and no fundoplication, 7 of them were managed on medical therapy alone with good outcomes.[35] The other two required fundoplication later in life. It is suggested that fundoplication in these instances be reserved for GERD resistant to medical therapy.

Diagnostic testing

Monitoring for GERD is necessary as it contributes to patient morbidity, given potential complications of dysphagia, esophagitis, BE, silent aspiration, aerodigestive complications, failure to thrive, and stricture formation. Having an efficacious way to monitor for GERD can help patient selection for PPI therapy and help to determine the duration for which it should be continued. Endoscopy, pH testing and pH-impedance testing all have a role in diagnostic testing, each with their own pros and cons (Table 1).

Endoscopy—Endoscopy has the ability to monitor for evidence of GERD, treatment failure, and complications of GERD, such as erosive esophagitis, strictures, and Barrett's Esophagus (BE). On endoscopy, visualizing endoscopic breaks in mucosa is the most reliable evidence of reflux esophagitis. [36] Histologic findings of GERD, which include basal zone hyperplasia, papillary lengthening, and neutrophilic infiltration,[37] are not specific to GERD alone and do not always correlate to symptom severity in children.[38] The sensitivity of histologic changes increases when multiple biopsies are taken, and is reported up to 96% in patients with erosive esophagitis and 76% with non-erosive reflux disease.[39]

In addition to establishing the diagnosis of GERD, endoscopy allows for the identification of complications of GERD.[40] Although are no studies that have evaluated the utility of routine endoscopy in EA patients, multiple studies show that patients with EA are at increased risk for GERD complications, some of which cannot be diagnosed without endoscopy. EA patients with distal TEF (type C) and EA patients with both proximal and distal TEF (type D) are at maximal risk for moderate to severe esophagitis and/or gastric metaplasia at ages 3 to 5 years old, though these can happen at any age. The risk becomes low after 6 years of documented normal biopsies. [41, 42]

Asymptomatic EA patients can also have endoscopic esophageal changes. In a retrospective study of 209 patients with repaired EA/TEF who underwent surveillance biopsies at 1, 3, 5, 10, and 15 years, metaplasia was present in 33% patients on endoscopy after 15 years, mild esophagitis occurred in about 1/3 of patients in surveillance endoscopy across all years, and moderate esophagitis fluctuated between 5-11%.[43] Given that only 9% of patients with metaplasia and 32% of patients with moderate esophagitis were symptomatic, scoping only

symptomatic patients could miss patients who have moderate to severe pathology.[6] Based on expert opinion, surveillance endoscopy is recommended upon stopping PPI therapy, before 10 years of age, and on transition to adulthood.

When upper endoscopy is performed, the following areas should be carefully examined: upper esophagus, as EA patients are at increased risk of inlet patch;[44] esophagogastric junction; and the anastomosic site. The endoscopist should also be looking for stenosis, diverticulum or fistula, hiatal hernia, peptic changes, or findings suggestive of eosinophilic esophagitis. At least 4 biopsies, in quadrants, should be obtained regardless of whether the esophagus appears macroscopically normal, as this is optimal for screening of both eosinophilic esophagitis and Barret's esophagus. If macroscopic abnormalities are seen, more biopsies may be warranted.

pH probe testing—pH probe testing has high sensitivity in predicting erosive esophagitis in adults and children, ranging from 83-100%.[45, 46] Clinically important acidic pH is considered <4, and the reflux index (RI) is defined as the percentage of study duration that the pH<4. Pediatric guidelines have defined the RI upper limit of normal to be 7%, an RI < 3% to be normal, and an RI between 3% and 7% to be indeterminate.[36] Limitations to standard pH monitoring include being unable to detect weakly acid (pH 4-7) or nonacid (pH>7) reflux,[47] and overestimating acid exposure by picking up "pH-only" episodes, in which there is no detected liquid reflux.[48] Infants and children have weakly acidic reflux more often than adults,[48, 49] and this may explain why esophageal pH monitoring may not always correlate with their symptoms.[45]

Koivusalo et al. showed, in a study of 90 patients with EA, that pathologic pH monitoring results at an early age (mean age 9 months) predicted the development of GERD associated with esophagitis or requiring antireflux surgery. This suggests a benefit of early pH monitoring in the symptomatic patient.[50] Importantly, it was noted that a normal early pH test does not rule out the development of GERD. While normal values for pH probe testing are not available in EA patients, parameters such as reflux index, total number of reflux periods with pH<4, and numbers of periods of pH<4 lasting more than 5 minutes are similar in EA patients to those in normal infants of the same age.[51] Therefore, pH probe testing is recommended for infants ages 9 to 12 months of age to screen for GERD.

pH-multichannel intraluminal impedance (pH-MII)—Multichannel Intraluminal Impedance (MII) utilizes change in resistance to content in the esophagus to measure bolus transit. It can detect the direction of movement – anterograde versus retrograde – thereby distinguishing between reflux and swallows. It can differentiate intraesophageal content state – fluid, solid, and air – and can determine the height of the refluxate. Dual pH-multichannel intraluminal impedance (pH-MII) is additionally able to distinguish acid from nonacid refluxate.[52, 53] MII provides information about clearance of refluxed material. After an acid reflux episode, effective clearance is necessary to prevent against esophageal mucosal damage. Clearance of acid reflux is a two-step process:[54–60] a rapid volume clearance involving primary and secondary peristalsis, and slow chemical clearance accomplished primarily by bicarbonate-rich saliva that neutralizes acid.

While pH probes can be used to correlate symptoms with acid reflux, pH-MII probes are useful in correlating events with acid and non-acid reflux. This is relevant in EA patients, since many of them, particularly infants, are on acid suppression and continuous feeds.[52] Multiple studies have shown that reflux in EA patients is largely nonacid[61] or weakly acid.[62] One study showed that EA patients did not have a significantly different number of reflux episodes compared to controls, but did have a significantly larger number of non-acid reflux episodes.[62, 63] The benefit of using pH-MII in EA patients is further seen when comparing the Symptom Index (SI) to that calculated by pH-probe alone. The SI is defined as the percentage of symptoms associated with reflux, with a score of >50% being abnormal. Studies have found that EA patients tested with pH-MII result in a positive SI significantly more than when tested with pH probe alone.[64]

pH-MII can be used to quantify the frequency of “high reflux,” or the proportion of reflux reaching the proximal esophagus. EA patients frequently experience respiratory complications relted to GER, such as recurrent bronchitis, cough, choking, heartburn, and cyanotic episodes.[65] These can be a result of tranchomalacia, swallow dysfunction, or GERD reaching the proximal esophagus. pH-MII has the ability to determine if these symptoms correlate with reflux, regardless of acidity. Cough has been associated with reflux in 47-62% of EA patients,[61, 62] with high refluxes being both weakly acidic and acidic.[62] Children less than one year old more commonly had non-acid reflux related to cough, as opposed to children over one year old, who more frequently had acid reflux related to cough.[61]

Reference values for reflux parameters in infants and children are established based on data from pH-MII studies over a 24-hour period.[66–68] In EA patients in particular, pH-MII studies have a 75% lower baseline impedance than control patients.[62, 63] As a result, software analysis often misses reflux events, resulting in underreporting of reflux, and manual analysis must be done.[6]

Anastomotic strictures

Anastomotic strictures are still the most common complication following operative repair of EA.[16, 69] Despite the identification of several risk factors for such strictures, such as long-gap EA with consequent anastomotic tension, postoperative anastomotic leak, and GERD, both intra- and post-operative prevention strategies have failed to significantly decrease the incidence of these anastomotic strictures over time. [70] [71] [14]

Data coming from literature show a high variability in anastomotic stricture incidence. While most studies report an incidence between 32 and 59%, [69] [16] [14] [72] [73] [74] others have reported an incidence as low as 5% or as high as 80%. The difference is likely due to varying definitions of anastomotic strictures and in differences among centers regarding patient populations’ risk factors for development of these strictures (e.g., long gap EA). The rate of anastomotic strictures is high in the first year after EA repair, with one study reporting need for a single dilation of anastomotic stricture in 68% of patients and serial dilations in 36% within the first postoperative year.[75]

Esophageal strictures are luminal narrowings of the esophagus that result in symptoms. Symptoms can vary and depend on the child's age and type of food ingested.[6] They can range from difficulty swallowing to airway complications resulting from aspiration. It is worth emphasizing that both the gastrointestinal and the respiratory symptoms that are seen with anastomotic strictures can be similar to those seen in other pathologic conditions that are prevalent in EA. These include esophageal dysmotility, airway reactivity, tracheomalacia, eosinophilic esophagitis, and laryngeal clefts.[76] It is therefore important that EA patients be evaluated at regular intervals to assess for and treat other comorbidities. [6]

Barium and other contrast imaging of the esophagus and/or endoscopy are recommended to diagnose these strictures [6] [77]. Once the presence of an anastomotic stricture has been established, the primary goal is to provide symptom relief and the mainstay of treatment is mechanical dilation.[6] The degree of esophageal narrowing does not correlate with symptoms and there is no conclusive evidence as to what the goal luminal diameter should be, based on patient age. Two categories of dilators can be used: fixed-diameter push-type dilators (bougie dilators) and radial expanding balloon dilators.

Fixed-diameter push-type dilators of increasing diameters are introduced via the oropharynx into the esophagus. They exert radial forces, but also a longitudinal force that causes a shearing effect as they are advanced through the stenosis. Currently, the most popular fixed-diameter push-type dilators are the guidewire-assisted polyvinyl Savary-Gilliard dilators. These are re-useable, and more cost-effective than balloon dilators.

With balloon dilations, the catheter can be inserted endoscopically or over a guidewire with fluoroscopic guidance. The balloon is inflated up to a desired pressure for 60 seconds, and the dilation is monitored under fluoroscopy. Balloon dilators only exert radial forces when expanded within a stenosis. These forces are delivered simultaneously over the entire length of the stenosed segment rather than progressively from its proximal to its distal extent [78]. While balloon dilation is done under fluoroscopy, which provides visualization of the dilation, no clear advantage between the two techniques has been demonstrated; therefore the choice between techniques is based on operator experience and comfort with the equipment.[6]

Two main "philosophies" have been adopted in clinical practice regarding the interval between the dilation sessions: 1) prophylactic routine dilation/calibration to prevent symptoms developing;[79] 2) selective dilations only when the symptoms arise.[14] Koivusalo et al. retrospectively demonstrated that routine dilations had equal long term outcomes as selective dilations with respect to dysphagia, bolus obstruction, and nutritional status.[80] In addition, performing dilations only when patients had symptoms resulted in significantly fewer dilations and, as a result, fewer complications from dilations. The most frequent complications of dilations include perforation, hemorrhage, and bacteremia. Recent European and North American Societies for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN and NASPGHAN) recommendations agree with the above study, stating that there is no evidence to support the use of routine dilations. They do advise,

however, that patients with long gap EA and postoperative anastomotic leak need close follow-up to avoid development of severe AS [6].

Certain patients with EA may experience recurrent and refractory anastomotic strictures, despite dilation treatments. Baseline conditions as well as intra- and post-operative conditions contribute to stricture outcome. For strictures refractory to esophageal dilation, conservative management is preferred prior to proceeding to surgery. Several adjunctive treatments have been used to minimize the risk of stricture reoccurrence following dilation. Overall, most data on nonsurgical adjuvant treatments are derived from studies on adult benign strictures or children experiencing refractory caustic strictures. Data on anastomotic strictures in EA patients are scarce and heterogeneous, and large prospective studies are needed to better define feasibility, safety, and efficacy in this group of patients.

Local injection of steroids[81] [82] and topical application of Mitomycin-C into the stricture site[83] have showed encouraging results, but long-term studies are needed to prove their efficacy and safety. Esophageal stenting (plastic or metal stents) has been reported to be effective in preventing stricture recurrence,[84, 85] [86] but additional evidence is required to confirm these data. For anastomotic strictures refractory to all forms of treatment, stricture resection followed by primary esophageal anastomosis or esophageal replacement with an interposition graft remain as options.[80, 87]

Eosinophilic Esophagitis

Recent studies report a higher prevalence of eosinophilic esophagitis (EoE) in EA patients compared to the general population.[88, 89] The largest reported number was in a study by Dhaliwal' *et al.*,[88] which reported a 17% incidence in a retrospective review of biopsies taken from 103 EA patients over a 13-year period. This is greater than the reported incidence of EoE in the general pediatric population (1 in 10 000 children), and in children with suspected GERD refractory to antireflux treatment (8% to 10%).[90] The higher incidence of EoE in the EA cohort has been ascribed to a possible genetic association, impairment of esophageal mucosal barrier function by acid refluxate, and prolonged exposure to acid suppressive medication.[88]

Identifying EoE in EA patients is integral to management, as EoE can present with similar symptoms as GERD, and long-term complications of untreated of EoE include dysphagia and strictures. Dhaliwal et al.'s study compared EA patients with and without EoE. EA patients with EoE had significantly higher incidences of symptoms of vomiting, dysphagia, or cyanotic spells, and also had significantly higher incidences of fundoplication and gastrostomy for feeding difficulties.[88] In this study, 38% had a stricture at the time of EoE diagnosis, and a significantly larger number of patients developed late strictures (i.e., after 1 year of age) compared to EA patients who did not have EoE. The relative risk for stricture formation in EA patients with either EoE or large gap atresia was 1.9, and with both EoE and large gap atresia was 4.[88] Other studies have reported a similarly high prevelance of strictures when EA was accompanied by EoE.[91–94]

Diagnosis of EoE in EA patients is similar to that in the general population and requires the presence of hypereosinophilia (>15 eosinophils/High Powered Field) in patients on high-dose acid suppression with PPIs. Multiple esophageal biopsies need to be taken, in keeping with standard guidelines for diagnosis of EoE, as EoE is a patchy disease process.[90] Also, typical macroscopic endoscopy findings, such as trachealization, furrows, and exudates, are not always present.[88, 91–93]

There is no evidence that the treatment and management of EoE in EA patients should be different from that in children without EA. Therefore current recommendations for treatment of EoE in the general population should be followed in EA patients.[95, 96] The only study to look at outcomes post-treatment of EoE in EA patients, by Chan *et al.,*[97] reported that during a median follow-up of 23 months, treatment of EoE resulted in an improvement, not only in intraepithelial eosinophilic density, but also in symptoms of dysphagia and reflux, prevalence of strictures, and need for dilations.[91]

Dysphagia

Dysphagia is estimated to be prevalent in 21-84% of patients with EA after surgical repair. [6, 98] When evaluating a patient, structural and inflammatory causes should be excluded first. There are pros and cons to each testing modality (Table 2).

Initial evaluation

Esophogram is a noninvasive test that allows for evaluation of strictures (anastomotic or peptic), recurrent fistulas, vascular ring, or congenital esophageal stenosis.[99] If esophagram is negative, endoscopy should be pursued to evaluate for peptic and eosinophilic esophagitis, a mucosal bridge, or a tight fundoplication. Dysphagia can also be a manifestation of aspiration, and video fluoroscopic swallow study should be performed to assess for this. If the workup continues to be negative, further evaluation with esophageal manometry is warranted.

High resolution manometry

Studies using high resolution manometry (HREM) show that almost all patients with EA have some degree of dysmotility.[63, 100] In a study of 40 pediatric EA patients, HREM revealed three different esophageal motility patterns: *aperistalsis*, *pressurization*, and *distal contractions*.[100] Dysphagia was present in all three groups. GERD-related symptoms were predominant in the aperistalsis group. In another study of 59 patients, HREM showed esophageal dysmotility in all patients, with 83% having no propagating swallows.[101] Of these 59 pediatric patients, 56% had GERD symptoms, 70% had dysphagia, and 56% had respiratory symptoms. In both infants and adults, transient lower esophageal sphincter relaxation (TLESR) is the most common mechanism underlying reflux episodes,[102] with no clearing mechanism initiated in 66% of reflux episodes. While characterizing the dysmotility pattern is helpful in EA patients, there are no studies on outcomes when modifying therapy based on HREM results.

Though the underlying cause of dysmotility remains unclear, the fact that esophageal dysmotility was shown to be present even prior to EA surgical repair in a study on 20

newborns with EA[103] suggests that dysmotility is congenital, likely due to abnormal development of the esophagus. These patients had one or more of the following prior to repair: incomplete relaxation of the upper esophageal sphincter, reduced or incomplete relaxation of the lower esophageal sphincter, or abnormal resting pressure of the esophageal body.

New investigative modalities

While esophageal manometry allows for identification of esophageal motility disorders, the relationship between esophageal contraction patterns and bolus transit interruption are unclear. High-resolution manometry with impedance has combined manometry and impedance probes, providing additional information on bolus transit.[104] This, along with automated impedance manometry analysis, allows better detection of bolus flow impairment, which in turn correlates well with patients' symptoms of dysphagia.[105] This technique is also more sensitive in detecting subtle abnormalities in esophageal function in patients with non-obstructive dysphagia and normal manometry.[106] The swallowing risk index can be calculated from this technique, and aims to quantify the overall level of swallowing dysfunction that potentially predisposes a person to the risk of aspiration.[107] It is calculated by the following formula: [Flow Interval x Pressure at time of nadir impedance]/[peak pharyngeal x (pressure time nadir impedance to peak pressure +1)] x 100. A swallowing risk index <8 is considered normal. There are no published data using these techniques in the EA population.

Feeding and Nutrition

Addressing feeding and nutrition needs of TEF/EA patients is critical and multidisciplinary teams have brought feeding and nutritional issues to the forefront of care. Interestingly, despite the feeding difficulties described in patients, there is an imperfect relationship between feeding difficulties and nutritional deficiencies. The rates of feeding difficulties vary by study and range between 6 and 79% of patients, depending on the age and the developmental stage of patients surveyed,[108–112] though only 13% of patients report being on a modified diet including thickened feeds (commonly used to treat reflux and/or oropharyngeal dysphagia).[75] As children age, the rates of feeding difficulties drop, with rates as low as 10% or less in teenagers.[113] Symptoms of feeding difficulties include food refusal, slow feeding, texture refusal, coughing during or after feeding, gagging or retching during or after feeding, vomiting, feeding slowly, refusing meals, coughing or choking during eating, and vomiting with meals. In a study of 75 children with EA/TEF by Menzies et al., almost 80% of children had at least one mealtime issue, with the most common abnormality being avoidance of developmentally appropriate textures. These texture issues improved over time; while 72% of infants and toddlers reportedly had texture issues, only 30% of children over the age of 5 had texture issues. Feeding questionnaires, however, may not represent more episodic feeding issues; 69% of patients report having had at least one food impaction[111] suggesting that texture issues may be episodic and not reported at routine visits. The etiology of these feeding issues is complex; Menzies et al. comment that there was no relationship between abnormal feeding patterns and the presence of malnutrition, gastrointestinal symptoms or respiratory symptoms suggesting that behavioral

feeding interventions (rather than escalating medical interventions) may be important predictors of feeding success.[108]

Concurrent with feeding therapy, it is important to understand some of the potential barriers to successful feeding. In infancy, feeding difficulties can results from: (1) oropharyngeal dysphagia/aspiration related to vocal cord paralysis, laryngeal clefts, associated congenital anomalies, neurologic compromise or developmental delays in swallowing; (2) aversions related to prolonged periods of fasting or tube feeding; (3) esophageal dysmotility; (4) esophageal obstruction related to stricturing or fundoplication; (5) discoordination between the suck-swallow-breath sequence in children with respiratory distress; (6) esophageal inflammation related to infection, reflux or eosinophilic esophagitis; and/or (7) vomiting related to gastroesophageal reflux disease, gastric dysmotility or medications. In older children, the etiologies are similar, though long-term dysmotility and persistent esophageal inflammation become bigger contributors once the acute issues (i.e. stricturing, respiratory distress, prolonged fasting postoperatively) are resolved.

Despite the potential multifactorial contributors to feeding difficulties, gastrostomy tubes are only used in 6-30% of patients beyond infancy[108] and the overall long term nutritional and feeding prognosis is good.[108, 109] Even in the patients with long gap atresia, patients reach their major feeding milestones in a similar pattern to normal control infants,[114] though some investigators have found a delay in solid food introduction by 8 months or longer.[112] In a parent-completed questionnaire, Baird et al. found that only 6.7% of patients had feeding scores greater than two standard deviations above the mean and the majority of these feeding difficulties were reported as mild.[110] Reflecting this mild spectrum, only 11% of patients report feeding concerns to their care providers.[112]

Despite the medical complexities of these patients, the nutritional status of patients is infrequently compromised. Menzies et al. report that only 18% of children had a weight-for-age Z score >2 standard deviations from the mean, 9% had a weight-for-length Z score >2 standard deviations from the mean, and 9% had a length for age >2 standard deviations from the mean.[108] Similarly, Deurloo et al. found that 7% of patients were below the 5th percentile for height and/or weight, with associated comorbidities predicting a worse nutritional prognosis.[115] Finally, Legrand et al. similarly report excellent growth parameters, with 91% of patients normal or overweight.[15] These findings suggest that despite significant mealtime struggles, families are persistent and successful in maintaining patients' nutritional status by picking up on their children's cues, modifying their diet and environment, and persisting with feeding, even when difficult.

Extraintestinal Manifestations

Respiratory complications are common in children with EA, with patients often presenting with wheezing, cough, choking, and recurrent respiratory infections. These symptoms are often the result of tracheomalacia and aspiration due to swallowing dysfunction or gastroesophageal reflux.[116, 117] Comorbidities that can impact the respiratory system can be grouped into the following:

1. Functional and structural anomalies of the upper respiratory tract: Tracheomalacia, laryngeal cleft, subglottic stenosis, vocal cord paresis or immobility
    - Tracheomalacia: This is the most common structural tracheal defect in EA-TEF, present in up to 78% of patients.[116] The severity depends on the extent of weakness or absence of tracheal cartilage. Symptoms include feeding intolerance, barking cough, expiratory stridor, unresponsiveness to medical treatment, delayed recovery from respiratory infections, and occasionally apneic or cyanotic spells.[118]
    - Laryngeal cleft: symptoms include recurrent wheezing, dysphagia, aspiration, or pneumonia
    - Vocal cord abnormalities:[119] symptoms include aphonia or dysphonia, weak/hoarse cry, stridor, dysphagia, coughing with feeds
2. GI tract problems: GERD, esophageal dysmotility, esophageal strictures
    - GERD: As discussed earlier, EA patients are at a higher risk of GERD due intrinsic anatomic abnormalities, post surgical anatomy alteration, and altered motility from disturbed intrinsic innervation. Reflux reaching the proximal esophagus and airway can lead to respiratory symptoms.[11, 99]
    - Dysmotility and Strictures: Pooling of food and secretions due to esophageal dysmotility and/or strictures can lead to aspiration. Strictures could be due to anastomotic tension, reflux, or EoE.
3. Lower airway abnormalities: bronchiectasis, increased bronchial responsiveness
    - Bronchiectasis: Recurrent bouts of lower respiratory tract infections cause bronchiectasis to develop. EA patients are at high risk for this, given their high rates of lower respiratory tract infections in the first years of life, with more than 5 such infections reported in the 1st year of life.[120]
    - Increased bronchial responsiveness: This has been described in 22-65% of EA patients, and is thought to reflect damaged airway epithelium from recurrent acidic aspiration.[121]

GI and pulmonary symptoms are interrelated, and there should be a focus in identifying risk factors and treating them early. In a study of long term follow up of 27 EA patients, 63% showed abnormal lung function at rest or after exercise, 41% had restrictive ventilator defects, 48% had obstructive or combined defects.[122] Restrictive ventilator defects correlated with the interpouch distance, GERD, and recurrent pneumonia during infancy. This study highlights the importance of identifying risk factors such as GERD early on, to prevent long term affects on respiratory function. It also shows the need to have regular follow up with these patients in order to detect the presence and progression of respiratory complications.

Children need to be evaluated by a multidisciplinary team, including gastroenterology, pulmonology, and otolaryngology and speech pathology, regardless of symptoms, as patients can often go misdiagnosed if not evaluated by all specialties. In a study of 29 children with EA, 72% had cough, 55% had dysphagia, and 34% had recurrent pneumonia. When evaluated by a multidisciplinary team, all the children in this study were found to have tracheomalacia, and multiple others had their diagnosis changed resulting in a change in medications.[123] A separate study showed how respiratory symptoms are often overlooked in children with repaired EA.[124] When evaluating lung function in 31 children, 45% of them had poor ventilatory response, and of these children, 77% were not on any pulmonary directed treatment.

Evaluation of pulmonary complications can be achieved by an array of testing, though there are no guidelines as to how frequent routine monitoring should take place. Spirometry allows for identification of pulmonary function disturbances,[125] and can guide the need for further testing. Flexible and rigid bronchoscopy allow for evaluation of presence and severity of tracheomalacia and for findings suggestive of GERD such as erythema or edema of the airway and presence of inflammatory cells on the broncheoalveolar lavage .[121] Lavage fluid also allows for identification of pathogenic organisms diagnostic of chronic pneumonia.[123] Laryngoscopy allows for identification of laryngeal cleft and subglottic stenosis. Chest computerized tomography may be indicated in chronic pulmonary symptoms and infections to help identify bronchiectasis, pneumonia, and atelectasis. Given that proximal reflux may lead to aspiration pneumonia, anatomic defects such as strictures and dilation can be evaluated by an esophagram. Upper endoscopy can further evaluate for esophagitis caused by GERD or EoE that may be causing similar symptoms. pH-impedance is a more specific method to correlate pulmonary symptoms with GERD, but has limitations, as discussed earlier. Video fluoroscopic swallow study should be performed as well if there is a suspicion for aspiration.

Associated Gastrointestinal Conditions in Children with EA

Approximately 50% of EA patients have one or more other gastrointestinal anomalies – generally as part of the VACTERL association (vertebral, ano-rectal malformations, cardiovascular, renal and limb anomalies).[126] The incidence of gastrointestinal anomalies, excluding ano-rectal malformations, in association with EA, varies from 3.6% to 7.5%.[127]

Hypertrophic pyloric stenosis.

Pyloric stenosis occurs in approximately 1 in 400 live births in the western hemisphere population.[128, 129] The 7.5% incidence of pyloric stenosis in EA patients reported by Van Beelan was 30 times higher than its 0.25% incidence in the normal population.[129] The diagnosis was generally delayed, by a median of 6 days (range, 1–21 days).[130] Hypertrophic pyloric stenosis was diagnosed during ultrasound, contrast study, or surgical procedures.[130]

Malrotation.

The reported incidence of malrotation in EA patients has ranged from 8.6-12.7%.[127] There is often a delay in diagnosis and there are reports of death due to volvulus.[127] In EA patients, often only the anastomosis is imaged, as a result of which a malrotation can be missed. Upadhyay felt that contrast studies should include the duodenum to note the rotation of the bowel, and at the time gastrostomy is performed, along with searching for other atresias, one should look for malrotation of the small intestine.[131]

Heterotopic Gastric Mucosa (HGM).

A well-defined area of HGM or “inlet patch”, typically located in the proximal esophagus just inferior to the upper esophageal sphincter,[132] has been reported in up to 34% of patients with EA[133] versus 0.1% to 10% in adults and up to 21% in children.[132] HGM has been reported in up to 34% of patients with EA.[133] Four cases of HGM at the anastomotic site have been reported .[133–135] HGM is typically considered a benign finding, but studies show acid secretion from HGM can occassionally cause symptoms,[136] including mild dysphagia, gastrointestinal bleeding, ulceration, fistula formation, stricture, malignancy, cough, wheezing, and asthma.[135] Proton pump inhibitors and esophageal dilations have been successful in treating symptomatic HGM.[135]

Congenital esophageal stenosis.

Congenital esophageal stenosis is rare, with a reported incidence of 1 in 25,000 to 50,000 live births. While the defining characteristic of congenital esophageal stenosis is intrinsic circumferential narrowing of the esophageal lumen present from birth, symptoms may not manifest in the neonatal period. An embryologic origin has been implicated, but the exact etiology is unknown. There are three histological types of of such congenital stenoses: ectopic *tracheobronchial remnants* in the esophageal wall segmental *fibromuscular hypertrophy* of the muscle and submucosal layers, and a *membranous diaphragm or stenosis*. Dilation may be effective for treating patients with either of the latter two, but surgical repair is often required for those with tracheobronchial remnants. [137] In about half of cases, congenital esophageal stenosis is associated with EA. [137, 138] In these cases, diagnosis of the congenital stenosis is often delayed.

Duodenal Atresia/Duodenal Stenosis.

Of the gastrointestinal anomalies associated with EA, studies suggest that the most lethal combination is that involving duodenal atresia.[139] The association of EA and duodenal atresia or stenosis is well recognized, although uncommon.[139, 140] In babies with EA-TEF, coexisting duodenal obstructing lesions can usually be diagnosed based on plain films of the chest and abdomen. In those with pure EA, the diagnosis may be subtler and may require ultrasound or contrast studies.[141] Quite often, the duodenal lesion is not appreciated until esophageal continuity is established, or when gastrostomy feedings fail. [142] The timing of surgical repair of duodenal atresia or stenosis is controversial. Both Spitz and Ein felt that a delayed repair of such duodenal lesions affords babies with prematurity and respiratory distress the opportunity for improvement in growth and

maturation of pulmonary function. In addition, it allows for some resolution of the delayed gastric emptying often seen after repair of duodenal atresia or stenosis.[141, 142]

Heterotopic Pancreas.

Heterotopic pancreas is defined as pancreatic tissue lacking anatomical and vascular continuity with the pancreatic gland, which is most often located along the greater curvature of the prepyloric antrum. A prospective case control study in children with EA reported a significantly higher incidence of gastric heterotopic pancreas in 18.7% of EA patients compared with 0.5% in the control group.[143] Complications of heterotopic pancreas can include ulceration, gastric outlet obstruction, intussusception, pancreatitis, and, rarely, malignant transformation.[143] However in the cohort of EA with heterotopic pancreas followed carefully since 2005 in Moreau's study, none had developed complications related to the pancreatic tissue.[143]

Dumping Syndrome.

Dumping syndrome can occur after primary anastomosis of EA without anti-reflux surgery.[144] It can manifest as feed refusal, nausea, retching, pallor, lethargy, diaphoresis, and watery diarrhea.[145] Michaud et al. have reported the cases of 2 children with EA who presented with dumping syndrome without any known precipitating factors, such as fundoplication or associated microgastria.[144] Previous reports of dumping syndrome in EA had so far been related to fundoplication.[146] Abnormal gastric emptying is frequent in EA patients.[147–150] Both abnormal gastric emptying and/or damage to the vagus nerve during esophageal anastomosis may lead to dumping syndrome.[144, 146] An oral glucose tolerance test revealing early and/or late hyperglycemia can be used to diagnose dumping syndrome in EA patients.[144]

Congenital Diaphragmatic Hernia.

Association of congenital diaphragmatic hernia with EA is rare. Ben Ishay detected an associated EA in 0.5% of 4888 cases of such hernias; patients with both disorders manifested overall survival significantly lower than the registry mean survival rate for the hernias alone $p < 0.001$) [151]. Patients with both disorders also had a very high incidence of associated minor and major anomalies (82.6%) in this study [151].

Long Term Follow Up

Since the first successful operation was for EA was conducted in 1941, the first generation of patients operated on for EA are reaching their seventh decade of life, pointing out that EA is becoming more and more an adult health issue. Moreover, it is noteworthy that since the late 1960's more than 70% (and today >90%) patients survive and reach adulthood. Therefore, a growing number of EA survivors are adults. Hence, focus on long-term outcomes in these patients is necessary as well as education of physicians who have to follow them.

GERD continues to be reported frequently in adolescents and adults with EA, with symptoms of GERD being reported in 22-76% of these patients.[15, 117, 152–156] Quality

of life is significantly impaired in EA patients and reflux symptoms contribute to this reduced quality in children as well as in adults.[13] Chronic acid exposure increases the risk of Barrett's Esophagus (BE) with intestinal metaplasia, which in turn is a risk for esophageal adenocarcinoma. There is a 4 to 26 times higher prevalence of intestinal metaplasia in EA patients as compared to the general population, with prevalence ranging between 1.1 and 11.3%.[6, 157] Such BE sometimes presents even in infancy.[158] Males with EA over 35 years old and with GERD symptoms more than 3 times a week are at greatest risk of developing BE.[155] American College of Gastroenterology guidelines recommend starting surveillance endoscopy to evaluate for BE in men with chronic GERD if they have 2 or more of the following risk factors: age >50 years, Caucasian race, central obesity, current or past history of smoking, and a family history of BE or esophageal adenocarcinoma in a 1st degree relative.[159] However, since there is a significantly increased risk of BE in the EA population, with no studies evaluating the need for surveillance endoscopy, EA-TEF guidelines recommend surveillance endoscopy every 5 to 10 years and additional endoscopy if new or worsening symptoms are present.[6]

Dysphagia is the most common reported GI problem in adult patients with EA.[117] The prevalence of swallowing dysfunction in adults was reported to be 82% in one study that followed 97 EA patients 18-63 years following surgical repair.[98] GERD and esophageal strictures were present in some, but not all of these patients. Other reasons for dysphagia include abnormal esophageal motility, colonic interposition leading to stasis of food in the neo-esophagus, and ongoing esophageal strictures or narrowing.[117]

Data show that as children transition into adulthood, they continue to have multisystem problems.[116, 125, 160] Beside digestive symptoms of GERD and dysphagia, the most frequent symptoms reported are respiratory.[116] In a study following up on 101 adult patients, 41% had bronchial hyper-responsiveness, 15% had asthma, 21% had restrictive ventilatory defects, 21% had obstructive respiratory defects, and 36% had both restrictive and obstructive ventilatory defects.[161] Significant impairment in quality of life resulted from these symptoms. While respiratory problems are more frequent during childhood, studies have shown that chronic cough and wheezing do not improve with age.[72, 161] A study of 125 EA patients found that shortness of breath and respiratory infections were more common in the 16-20 year old age group than all younger age groups.[72]

Given that symptoms and complications persist into adulthood, transition of care from pediatric to adult services is imperative. Guidelines recommend that patients have ongoing follow up with general practice, gastroenterology, surgery, and pulmonology specialties.[6]

Abbreviations

BE	Barrett's Esophagus
EA	Esophageal Atresia
EoE	Eosinophilic Esophagitis

ESPGHAN	European Society for Pediatric Gastroenterology Hepatology and Nutrition
GERD	Gastroesophageal Reflux Disease
H2RA	Histamine-2-Receptor Antagonist
HGM	Heterotopic Gastric Mucosa
HREM	High Resolution Manometry
NASPGHAN	North American Society for Pediatric Gastroenterology Hepatology and Nutrition
MII	Multichannel Intraluminal Impedance
PPI	Proton Pump Inhibitor
SI	Symptom Index
TEF	Tracheoesophageal Fistula
TLESR	Transient Lower Esophageal Sphincter Relaxation
VACTERL	Vertebral, Ano-rectal malformations, Cardiovascular, Renal and Limb anomalies

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Table 1:

Benefits and Limitations of GERD testing modalities [45, 47, 52, 62]

	Benefits	Limitations
Endoscopy	• Detects erosive esophagitis • Can be used to monitor for treatment efficacy • Allows for detection of complications of GERD, including strictures and Barrett's Esophagus • Can detect eosinophilic esophagitis, which can masquerade as GERD	• Findings are suggestive of, but not specific to, GERD • Findings don't correlate well with symptoms
pH-only	• Quantifies frequency and duration of acid exposure • Measures chemical clearance • Can correlate acid reflux to symptoms • Readily available • Easier to interpret than pH-impedance	• Unable to detect non-acid and weakly acid reflux • Detects "pH-only" episodes, thereby overestimating acid • Limited utility in patients on acid suppression, continuous feeds, or frequent feeding schedule
pH-impedance	• Quantifies acid and non-acid reflux • Detects liquid, gas, and mixed refluxate • Measures volume and chemical clearance • Quantifies the height of refluxate • Better able to correlate respiratory symptoms to proximal reflux	• Reference values are not based on healthy children, but are likely to have physiologic reflux based on strict selection criteria • Unknown ideal time frame between symptoms and reflux events, and are likely different depending on symptoms being recorded • Analysis is time consuming • Low baseline impedance in EA patients makes it difficult for automated analysis to detect reflux events, and must be manually reviewed • Limited availability in certain medical centers and practices

Table 2:

Benefits and Limitations of dysphagia testing modalities

	Benefits	Limitations
Esophogram	• Detects strictures and structural anomalies ie recurrent fistula, vascular ring, congenital stenosis	• Radiation exposure
Endoscopy	• Detects strictures and esophageal inflammation • Endoscopic biopsies can differentiate between type of inflammation: peptic, eosinophilic, infectious, etc.	• Need for anesthesia • Can miss subtle stricturing
Video fluoroscopic swallow study	• Allows evaluation of aspiration in real time, with different consistencies • Occupational therapist can assess feeding behavior and techniques	• Radiation exposure
High resolution esophageal manometry	• Provides information on segmental esophageal peristalsis • Accurate information on bolus transit, including if structural resistance is present • Identifies patients with poor coordination between proximal and mid-esophagus • Identifies issues with upper and lower esophageal sphincter function • Can correlate symptoms to dysmotility findings in real time	• No studies on outcomes after modification of therapy made based on HREM • Limited availability at all centers