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Predictors of anti-reflux procedure failure in complex esophageal atresia patients

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Abbreviations: EA, Esophageal atresia
LGEA, Long gap esophageal atresia
ARP, Anti-reflux procedure
ARPF, Anti-reflux procedure failure
gerd, Gastroesophageal reflux disease
MFOIS, Modified functional oral intake scale
GEJ, gastroesophageal junction
HH, hiatal hernia
MIS, minimally invasive surgery
EGD, esophagogastric duodenoscopy
UGI, upper gastrointestinal series
SSI, surgical sight infection

ABSTRACT

Background: Anti-reflux procedures (ARP) in esophageal atresia (EA) patients can be challenging and prone to failure. These challenges become more evident with increasing complexity of EA. We sought to determine predictors of ARP failure in complex EA patients.

Methods: Single-institution retrospective review of complex EA patients (e.g. long-gap EA, esophageal strictures, hiatal hernia, and reoperative ARP) who underwent an ARP from 2002 to 2019. ARP failure was defined as hiatal hernia recurrence, wrap migration/loosening, or need for reoperation. Predictors of failure were evaluated using univariate and multivariable time-to-event analysis.

Results: 121 patients underwent 140 ARP at a median age of 13.5 months (IQR 7, 26.5). Nissen fundoplication (89%) was the most common ARP. Mesh (bovine pericardium) reinforcement was used in 41% of the patients. Median follow-up was 3.2 years (IQR 0.9, 5.8); 44 instances of ARP failure occurred (31%), though only 20 (14%) required reoperation. Median time to failure was 8.7 months (IQR 3.2, 25). Though fewer mesh-reinforced ARP failed (21% with vs 39% without, $p = 0.02$), on multivariable analysis only partial fundoplication (aHR 2.22 [95% CI 1.01–4.78]) and minimally invasive repair (aHR 2.57 [95% CI 1.12–6.01]) were significant predictors of ARP failure.

Conclusion: In our practice of complex EA patients, where ARP fail in nearly one third of cases, a Nissen fundoplication performed via laparotomy provided the lowest risk of ARP failure.

1. Introduction

Gastroesophageal reflux disease (GERD) is common in children with a history of esophageal atresia (EA). Studies have reported GERD in 33% to 58% of EA patients [1–6], although this is likely an underestimate as the definition of GERD, and differences in endoscopic surveillance, are quite variable in children with EA [7–10]. Widespread use of antacid medications may also mask symptoms. In this population, GERD often results in delayed oral feeding, the inability to tolerate gastric feedings, respiratory infections, poor nutrition, and can adversely affect the healing of the esophageal anastomosis [8,11,12]. Treatment often includes postural and feeding modifications along with antacid and/or prokinetic medications. Despite these interventions, 17% to 73% of EA patients are deemed to have medically-refractory GERD and undergo an anti-reflux procedure (ARP) [1,7,13–16].

ARP in children following repair of EA present significant challenges which increase as the severity or complexity of EA increases; particularly in the setting of long gap esophageal atresia (LGEA) or previous failed fundoplication. Furthermore, EA patients generally have esophageal dysmotility and are at risk for post-ARP dysphagia. Additional challenges may include the presence of a hiatal hernia, microgastria, delayed gastric emptying, esophageal anastomotic stricture, and/or foreshortened esophageal length, all of which may impact the choice of ARP performed and its outcome.

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Various ARP techniques have been utilized to address the challenges posed by patients following EA repair. Partial anterior or posterior wraps, intussusception or Belsey type fundoplications, the Collis-Nissen procedure or even gastro-esophageal dissociations have been performed with varying degrees of success [17–19]. Despite its potentially greater risk of post-ARP dysphagia, the Nissen 360-degree wrap remains the most widely used ARP technique [2,20]. Many have reported outcomes of ARP in patients following EA repair with higher rates of failure compared to those in non-EA patients [21,22], with studies reporting ARP failure rates that range from 7.8% to 47% [2,13,20,23]. While others, Pellegrino et al., report finding no difference [1]. Despite this controversy, due to the multiple previously described challenges, we believe a higher rate of failure is likely. However, definitions of failure, surveillance protocols, and length of follow-up vary widely following ARP. In addition, controversy remains regarding which patients and at what age they would benefit most from an ARP. Similarly, predictors of ARP failure and strategies to mitigate them remain poorly understood [23].

In our practice of predominantly complex EA patients, ARP have been an integral part of their care. As our experience with this complex group has increased, we have sought to better understand what factors contribute to ARP failure. In this manuscript we evaluate the outcomes of ARP performed at our institution, the effectiveness of different ARP failure mitigation strategies and the many lessons learned along the way.

2. Methods

This is a single center retrospective review of all patients with a primary diagnosis of EA (any type) who underwent ARP between January 2002 and December 2019. Demographic, operative details, postoperative outcomes, complications, and details of revisional ARP were recorded from the medical chart. Pre-operative variables included indication, diagnostic work-up, history of prior ARP, timing of EA repair, history of Foker procedure, and pre-operative anti-acid medications. Indications included medically refractory GERD, anastomotic stricture management and aspiration pneumonia. We defined medically refractory GERD as persistent vomiting or regurgitation with feedings, inability to advance gastrostomy-tube feedings to goal, or dependence of gastrojejunostomy (GJ) tube feedings, and endoscopic evidence of erosive or histologic esophagitis despite maximal pharmacological therapy (e.g. proton pump inhibitors, histamine receptor blockers, prokinetics). The pre-and post-operative feeding status were determined using the modified Functional Oral Intake Scale (mFOIS, range 1–6 with 1–3 being entirely dependent on tube feedings, 5–6 being fully orally fed, and 4 and 4.5 being primarily orally fed but remaining partially dependent on tube feedings) [24–28]. The date of last follow-up was the last in-person or telehealth clinic visit.

2.1. Fundoplication technique

Our technique for Nissen fundoplication is as follows. We begin with wide exposure of the esophageal hiatus which often requires full mobilization of the left lobe of the liver, and if present, reduction of the hiatal hernia contents. Flexible endoscopy is then used to ascertain the location of the gastroesophageal junction (GEJ) and it is marked with a Prolene purse-string stitch to ensure the fundoplication is performed above that level. When present, a hiatal hernia is repaired prior to the fundoplication. The left and right crura are clearly delineated. If tissue quality is poor, we reinforce the posterior crural closure with a biologic permanent mesh (often bovine pericardium), incorporating the mesh into the closure as an onlay with vertical mattress sutures (Fig. 1a). In other words, the crura are brought together with the help of the mesh (similar to what a pledget-based approach would entail). First, we measure and trim the mesh to the desired length and width of the area to be covered by the mesh with about 1 cm of lateral overlap beyond the crura itself; this ends up being a roughly 3–4 cm long to 2–3 cm wide, horizontally oriented rectangular piece of mesh. Next, permanent sutures are placed in the following sequence (from lateral to medial): out-to-in the hiatus via the left crura, bottom-up through the mesh, top-down through the mesh and in-to-out the hiatus via the right crura, then back again in reverse order with smaller crural bites to complete the vertical mattress. It is easiest to place the sutures first through the crura and mesh (often 2–3 vertical mattress sutures are needed) and then parachute the mesh down and tie the sutures down at the end. A weight-based esophageal bougie is used to guide the extent of the crural closure [29]. We then place several, four to six, esophago-hiatus collar stitches to anchor the diaphragm to the esophagus cephalad to the GEJ to aim for at least two centimeters of intra-abdominal esophagus. The fundus of the stomach is then passed posterior to the stomach and anchored to the right crura with permanent sutures.

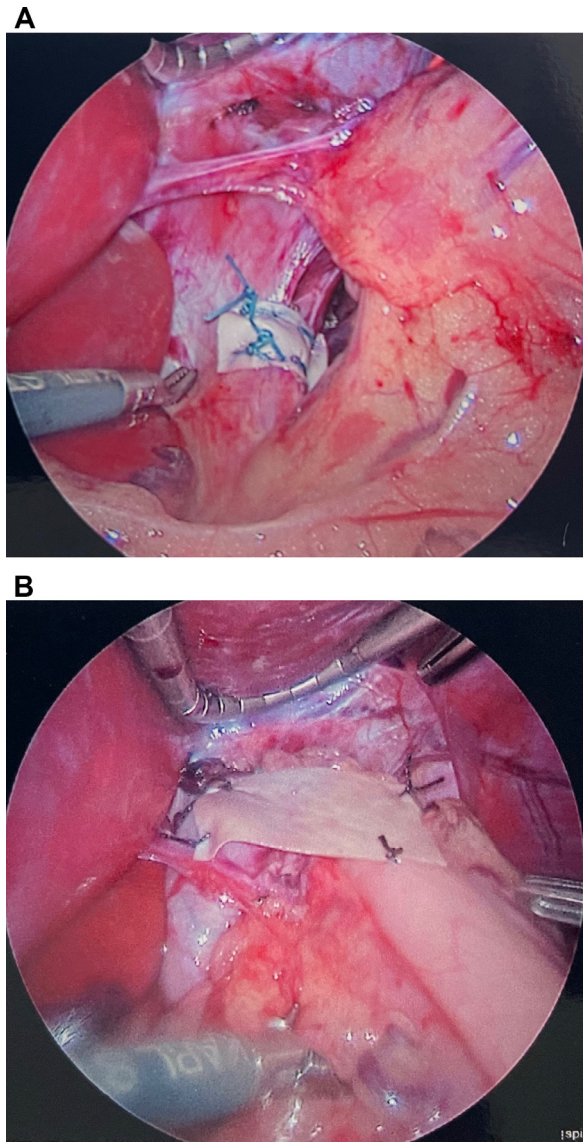

Fig. 1. a: Crural closure: If tissue quality is poor, a biologic permanent mesh (bovine pericardium) is incorporated into the crural closure as an onlay. **b**. Fundoplication: For cases at high risk of recurrence, a biologic permanent mesh (bovine pericardium) is placed in an onlay fashion to cover the fundoplication anteriorly.

Table 1
Demographic Variables.

Demographic Variables	N = 121 patients (%) or median (IQR)
Female	63 (52%)
EA type (Gross Classification)	
C	63 (52%)
A	39 (32%)
B	18 (15%)
D	1 (1%)
History of prior Foker procedure	63 (52%)
EA repair at BCH	66 (54%)
History of at least one previous Fundoplication at OSH	17 (14%)
Diagnostic Work-up Pre-Fundoplication*	
Flexible Esophagogastroduodenoscopy (EGD)	113 (92%)
Upper Gastrointestinal Contrast Study (UGI)	110 (89%)
Nuclear Medicine Gastric Emptying Study (GES)	31 (25%)
pH or Impedance Probe	4 (3.3%)
Preoperative Variables	N = 140 procedures (%) or median (IQR)
Age at Fundoplication (months)	13.5 (7, 26.5)
Weight at Fundoplication (Kg)	8.7 (6.3, 11.4)
Time interval between EA repair and Fundoplication (months)	7 (2, 24)
Indications[a]	
Medically refractory GERD	131 (94%)
Anastomotic stricture management	32 (23%)
Aspiration pneumonia	24 (17%)
Routine Post-Foker	10 (7%)
Hiatal Hernia	76 (54%)
Preop Feeding Status (median mFOIS, IQR)	1 (1,2)
Oral (no tube)	24 (17%)
Gastrojejunostomy tube	59 (42%)
Gastrostomy tube	53 (38%)
Nasogastric tube	3 (2%)
Nasojejunal tube	1 (1%)
Preop Anti-Acid Medications	
PPI only	60 (43%)
PPI and H2B	57 (41%)
H2B only	13 (9%)
Neither	1 (1%)
Unknown	9 (6%)

*patients could have more than one pre-op evaluation study or operative indication accordingly.
EA – esophageal atresia, BCH – Boston Children's Hospital, OSH - outside hospital, GERD – gastroesophageal reflux, PPI = proton pump inhibitors, H2B = Histamine receptor blockers.

Then, the medial or inner side of the fundus (facing the esophagus) is sutured to the esophagus on both sides (column stitches) to help prevent slipping and offload tension from the main fundoplication stitches to follow. The full 360-degree wrap is completed over the bougie and it is sutured in place to accommodate at least a 2 cm long wrap. Occasionally, for cases that are felt to be at high risk of recurrence, this wrap is reinforced with an onlay mesh (often bovine pericardium, see Fig. 1b). A rectangular piece of mesh, roughly 4–5 cm long by 3–4 cm wide is oriented vertically to cover the anterior portion of the fundoplication where the fundoplication sutures have been already placed. The corners of the mesh are anchored (off-tension) with small polypropelene sutures such that there is a 1–2 cm mesh overlap on each side of the underlying line of fundoplication sutures. The primary goal of the onlay mesh is to induce scarring on the anterior surface of the fundoplication. The wrap itself is then sutured to the diaphragm rim circumferentially (4–5 shoulder stitches). If a gastrostomy was present, it may be necessary to take it down at the beginning of the mobilization to allow for adequate exposure; in such a case, a gastrostomy resiting or revision is undertaken at the end of the case, if needed.

2.2. Postoperative surveillance

All of our EA patients undergo at least yearly endoscopic surveillance of their esophagus and fundoplication status in their first few years post-intervention. If asymptomatic, further evaluations are spaced out accordingly. If patients present with persistent or recurrent symptoms, then additional diagnostic evaluations are undertaken, such as an upper gastrointestinal contrast study.

2.3. Analysis

ARPF was the primary outcome of interest and defined as either hiatal hernia (HH) recurrence, wrap failure, or reoperation. HH recurrence or wrap failure (unwrapping) were determined by endoscopic or radiographic evaluation or operatively at the time of a revisional ARP. Asymptomatic HH recurrence or wrap failure detected incidentally at the time of endoscopic surveillance were also considered as ARPF.

Possible predictors of fundoplication failure included operative mesh reinforcement, history of Foker procedure, history of prior fundoplication performed at an outside institution, minimally invasive (MIS) operative approach, and use of endoscopic guidance. Additional operative details that were recorded included the technique for crural closure and wrap fixation, pyloroplasty or other concurrent procedures, management of the feeding tube during the operation and operative time. For those patients that underwent an elective ARP not performed during their initial hospitalization, hospital length of stay was included. For the majority of patients, however, ARP was performed as a continuation of care associated with their EA repair; for these patients, length of stay was not included in the analysis as ARP occurred prior to initial hospital discharge.

Descriptive and summary statistics are provided. Categorical variables are expressed as frequencies and percentages, while con-

Table 2
Operative and Postoperative Variables.

Operative Variables	N = 140 procedures (%) or median (IQR)
Type of Fundoplication	
Nissen	125 (89%)
Partial posterior	5 (4%)
Partial anterior	4 (3%)
Other*	6 (4%)
Operative Approach	
Laparotomy	105 (75%)
Laparoscopy	21 (15%)
Robotic	5 (4%)
MIS†→Laparotomy	9 (6%)
Crural Closure	
Sutures only	72 (51%)
Mesh Patch	40 (29%)
Pledgeted sutures	19 (14%)
None	9 (6%)
Wrap Fixation	
Sutures only	89 (64%)
Mesh Patch	50 (35%)
Pledgeted sutures	1 (1%)
Any Mesh Reinforcement	58 (41%)
Non-absorbable	55
Absorbable	3
Mesh Location	
Onlay wrap (anterior) and onlay crura (posterior)	34
Onlay wrap (anterior)	17
Onlay crura (posterior)	7
Endoscopic guidance to locate GEJ	90 (64%)
Pyloroplasty	10 (7%)
Gastrostomy tube approach	
Kept existing tube without modification	
Re-sited or revised existing tube	
New gastrostomy tube	
Remained without a G-tube	
65 (46%)	
45 (32%)	
15 (11%)	
15 (11%)	
Operative time (hours)	9 (7.4, 11.2)
Postoperative Variables	
Hospital length of stay (days)‡	9 (6, 17.5)

*Other= Intussusception or Mark-Belsey IV type via the chest.
†MIS = Minimally invasive surgery (laparoscopy or robotic approaches).
‡For patients being admitted only for the purposes of the fundoplication procedure and not undergoing other procedures (n = 37, 26%).
GEJ – gastroesophageal junction.

tinuous variables are expressed as medians (interquartile ranges). Univariate associations between demographic and operative variables with anti-reflux procedure failure (ARPF) were evaluated first with Fisher's exact test. Variables that appeared significantly associated ($p \leq 0.10$) with ARPF were then evaluated in a univariate time-to-event analysis using the log-rank test and Cox regression analysis and a multivariable Cox-regression model, where a p-value of <0.05 was considered statistically significant [30,31]. Cox regression analyses included a random effect for patient ID to account for multiple procedures per patient. The univariate analysis was reported as an unadjusted hazard ratio (HR) with corresponding 95% confidence interval (CI) and p-value while the multivariable Cox-regression model was reported as an adjusted hazard ratio (aHR) with a 95% confidence interval (CI) and p-value. Statistical analyses were carried out using Stata software version 16.0 (StataCorp LLC, College Station, Texas).

3. Results

During the study period, 121 patients were studied, 52% were female, 52% had a history of type C EA, 52% underwent a preceding Foker procedure, 54% had their EA repaired at our institution, and 14% had at least one prior fundoplication at an outside institution (Table 1). Among the 121 patients, 140 procedures were performed at a median age of 13.5 months. Among these 140 procedures, the primary indications for the ARP were medically refractory GERD (87%), esophageal anastomotic stricture management (23%), aspiration pneumonia (16%), and/or failed prior fundoplication (12%) with recurrent symptoms. The majority of patients underwent both a flexible esophagogastroduodenoscopy (EGD, 92%) and upper gastrointestinal contrast study (UGI, 89%) as part of the pre-operative diagnostic work-up. A hiatal hernia was present preoperatively in 76 patients (54%). Preoperative oral intake status for the majority of the cohort was poor with a median mFOIS of one (IQR 1,2); 116 patients (83%) were dependent on tube feedings with 40% requiring gastric and 43% requiring post-pyloric or jejunal feedings (Fig. 2).

3.1. Operative details

The median operative time (including associated procedures) was nine hours (IQR 7.4, 11.2, Table 2). The majority of ARP performed (89%) consisted of a full 360-degree Nissen fundoplication or wrap, while five partial posterior wraps (4%), four partial anterior wraps (3%), and six less traditional wraps (4%) were performed that included an intussusception and Belsey type fundo-

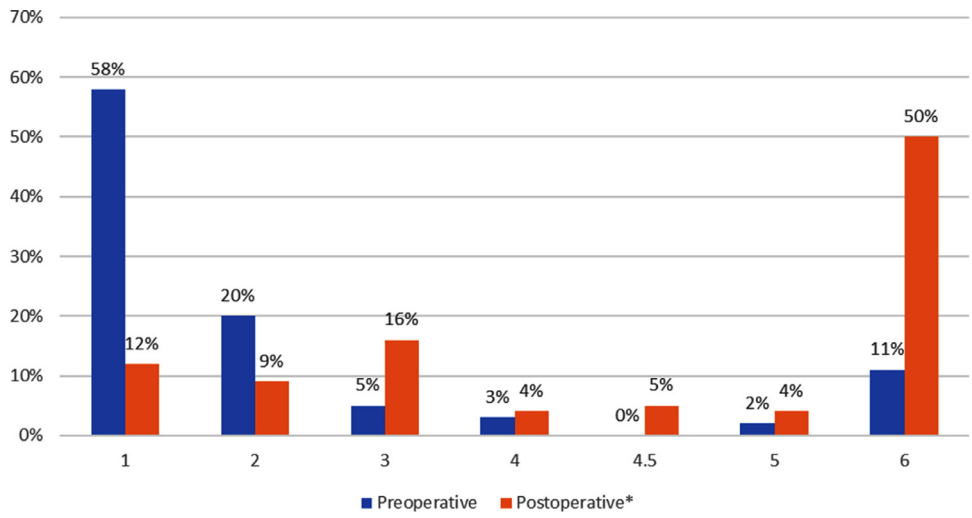

Fig. 2. MFOIS pre-op vs post-op
Comparison of modified Functional Oral Intake Scale(mFOIS) pre-anti-reflux procedure compared to the date of last follow-up. *Based on 121 patients, $n = 8$ have missing values postoperatively
Gastrostomy and/or jejunostomy dependent for nutrition with no attempts to feed by mouth
Gastrostomy and/or jejunostomy dependent for nutrition with inconsistent attempts to feed by mouth
Partially gastrostomy and/or jejunostomy dependent for nutrition (receiving any prescribed amount of tube feeds per day) with consistent (at least daily) successful attempts to feed by mouth
Minimal to no tube feeds, but require thickened liquids due to aspiration
Minimal to no tube feeds, no thickened liquids, but mash/blending solids or using high calorie formula by mouth to supplement
No tube feeds, no thickened liquids, eats all age-appropriate solid foods with minor accommodation (e.g. cutting food into smaller pieces, or requires sips of liquids in between solids)
No tube feeds, no thickened liquids, eats all age-appropriate solids without special accommodation
. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

plication. Seventy-five percent were performed with an open approach via laparotomy, while 15% and 4% underwent laparoscopic and robotic approaches, respectively. Six percent were initiated laparoscopically or robotically but required conversion to an open approach. The majority of crural closures and wrap fixations were performed with sutures only (51% and 64% respectively). Non-absorbable bovine pericardium mesh was used in 58 cases (41%). Of these 58 cases, 34 (59%) had mesh placed at both the wrap and crural closure, 17 (29%) at the wrap only, and 7 (12%) at the crura only. Endoscopic guidance to locate the GEJ was used in 64% of cases, and 10 procedures (7%) required a concurrent pyloroplasty at the time of the operation.

3.2. Follow-up

With a median length of follow-up of 3.2 years (IQR 0.9, 5.8), the feeding status of the cohort improved to a median mFOIS of five (IQR 3,6), where 46% were fed entirely orally, 47% had a gastrostomy tube in place and required varying levels of supplemental support, and eight patients (6%) continued to require either gastrojejunostomy or jejunostomy tube feedings due to persistent gastric intolerance (Fig. 2).

3.3. Complications

Of the 140 ARP performed, 44 failed [31%, defined as hiatal hernia recurrence or occurrence, wrap failure (becoming loose or undone), or reoperation, see Table 3] at a median of 8.7 months (IQR 3.2, 25). Of the 140, only 20 (14% of the total cohort but 45% of the recurrences) were symptomatic enough to require operative revision. Of patients with an ARPF, 32 patients (73% of ARPF) had a hiatal hernia occurrence or recurrence, and 21 patients (48% of ARPF) had a wrap failure (becoming loose or undone). Post-operative ARP dysphagia requiring endoscopic dilation of the wrap occurred in 33 (24%) patients (20% in partial fundoplication group versus 24% in the full Nissen fundoplication group, $p = 0.73$; 15% with mesh vs 12% without, $p = 0.6$), with a median of two dilations (IQR: 1,3) per patient with post-fundoplication dysphagia. In patients in whom bovine pericardium mesh was used ($n = 58$), we identified five (9%) intragastric mesh erosions. All erosions were asymptomatic and found incidentally during either surveillance endoscopy or re-operation for fundoplication failure. Superficial and deep surgical site infections (SSI) developed in 15 (11%) and seven (5%) cases, respectively. The use of mesh was not associated with the risk of developing a superficial (7% with vs 13% without, $p = 0.27$) or a deep SSI (3.5% with vs 6% without, $p = 0.7$). Eight patients ultimately required a jejunal interposition for esophageal replacement due to a dysfunctional or unsalvageable esophagus.

3.4. Predictors of fundoplication failure

Initial univariate analysis showed multiple significant predictors of ARPF including type of fundoplication (full 360 wrap (35%) vs partial (60%), $p = 0.01$), bovine pericardial mesh placement (with mesh (21%) vs with no mesh (39%), $p = 0.02$), history of Foker procedure (primary EA repair (23%) vs Foker procedure (39%), $p = 0.04$), use of endoscopic guidance to locate the GEJ (with endoscopic guidance (22%) vs without (48%), $p = 0.0002$), and minimally invasive approach (46% MIS vs 28% open, $p = 0.10$) (Table 4). On multivariable time-to event Cox regression analysis, both partial fundoplication (aHR = 2.22; 95% CI: 1.01, 4.78; $p = 0.045$) and MIS approach (aHR = 2.57; 95% CI: 1.12, 6.01; $p = 0.029$) were found to be significant predictors of ARPF (Table 5, Fig. 3a and 3b).

4. Discussion

This study represents one of the largest reported experiences with anti-reflux procedures in patients following repair of complex esophageal atresia. Our study results confirm the high rate of failure of ARP in this patient population; nearly one in every three

Table 3
Complications and Outcomes.

Complications	$N = 140$ procedures (%) or median (IQR)
Fundoplication failure*	44 (31%)
Hiatal hernia recurrence/occurrence	32 (23%)
Wrap failure	21 (15%)
Operative wrap revision	20 (14%)
Dysphagia requiring endoscopic dilation of wrap	33 (24%)
Number of wrap dilations	2 (1,3)
Superficial wound infection	15 (11%)
Deep/organ space infection	7 (5%)
Intragastric mesh erosion†	5 (9%)‡
	$N = 121$ patients (%) or median (IQR)
Outcomes	
Follow-up	
Endoscopic	113 (94%)
Contrast UGI	79 (65%)
Clinical length of follow-up (years)	3.2 (IQR 0.9, 5.8)
Feeding status, median mFOIS (IQR)	5 (3,6)
Oral	56 (46%)
Gastrostomy tube	57 (47%)
Gastrojejunostomy tube	5 (4%)
Jejunostomy tube	3 (2%)
Jejunal Interposition	8 (6%)
Postop Anti-Acid Medications§	
PPI only	73 (60%)
PPI and H2B	27 (23%)
H2B only	8 (7%)
Neither	5 (4%)
Unknown	7 (6%)

*Hiatal hernia recurrence/occurrence, wrap failure (becoming loose or undone), or reoperation.
†All asymptomatic and found incidentally either during endoscopy (and retrieved endoscopically) or during reoperation for fundoplication failure.
‡Percentage of those who had mesh placed or 58 patients.
§ At time of last follow-up.
IQR – interquartile range, UGI – upper gastrointestinal tract contrast study, mFOIS – modified functional oral intake scale, PPI – proton pump inhibitor, H2B – histamine receptor blocker.

Table 4
Univariate Associations with Antireflux Procedure Failure.

Variable	No Failure	Failed Fundo	p-value
Age at repair0–6 m6m-1y1–2y2–5y>5y	17 (59%)28 (74%)26 (70%)11 (65%)14 (74%)	12 (41%)10 (26%)11 (30%)6 (35%)5 (26%)	0.7
Weight at repair<5Kg5–10 kg10–15 kg>15kg	13 (72%)46 (67%)24 (73%)16 (80%)	5 (28%)26 (33%)9 (27%)4 (20%)	0.69
Previous fundoplicatonNoYes	73 (70%)23 (64%)	31 (30%)13 (36%)	0.53
Type of fundoplicationFull 360 NissenPartial or Other*	90 (72%)6 (40%)	35 (28%)9 (60%)	**0.01**
Type of esophageal atresiaCOther†	51 (71%)48 (68%)	21 (29%)23 (32%)	0.58
Foker historyNoYes	51 (77%)45 (61%)	15 (23%)29 (39%)	**0.04**
Use of meshNoYes	50 (61%)46 (79%)	32 (39%)12 (21%)	**0.02**
Mesh locationAnterior and PosteriorPosterior onlyAnterior only	29 (87%)4 (57%)12 (71%)	4 (12%)3 (43%)5 (29%)	0.11
Operative approachOpen or MIS→ OpenMIS₮	82 (72%)14 (53%)	32 (28%)12 (46%)	*0.10*
Preop hiatal herniaNoYes	43 (67%)53 (70%)	21 (33%)23 (30%)	0.75
Endoscopic Guidance to Locate GEJNoYes	26 (52%)70 (78%)	24 (48%)20 (22%)	**0.0002**

*Partial anterior, Partial posterior, Intussusception or Belsey type.
†Type A, B or D.
₮Laparoscopy or robotic approaches.
MIS – minimally invasive surgery, GEJ – gastroesophageal junction.

failed over time, consistent with the previously reported ranges of 7.8–47% [1,2,13,20,23]. However, not all ARPF were symptomatic enough to require reoperation. Many were discovered on routine follow-up EGD or contrast study of the esophagus. Significant predictors of ARPF were a partial fundoplication and a minimally invasive approach. It is also possible that performing the wrap at the level of the endoscopically located GEJ, and the use of mesh reinforcement, could play a role in preventing failures, though these issues warrant further study. Table 6 demonstrates many lessons learned overtime which are expounded on below.

In our experience, a partial fundoplication was never the preferred operative approach. It was performed only in patients with microgastria or those with severely damaged stomachs from prior operations where a full 360-degree Nissen fundoplication was not possible. Hence, we cannot conclude that a partial fundoplication in a normal sized stomach would lead to the poor rates of failure observed in our study. Proponents of a partial fundoplication cite the lower risk of post-operative dysphagia, which is an important consideration in EA patients who have varying degrees of baseline esophageal dysmotility [17,32–34]. In our study, the frequency of post-fundoplication dysphagia did not appear to be significantly different between the Nissen or partial fundoplication cohorts. Dysphagia was generally short-lived and resolved after a median of only two dilations. Clearly, one must individualize the risk of ARPF versus post-fundoplication dysphagia when considering a partial or a full 360-degree fundoplication.

Our fundoplication and hiatal hernia repair technique is the same whether it is done with an open or a minimally invasive approach. Though some have advocated in favor of the MIS approach for this patient population, we can only speculate that the worse

Table 5
Univariate and Multivariable Time-to-Event Analysis of Fundoplication Failure.

Univariate Analysis (Kaplan-Meier and Cox Regression)					Multivariable Analysis (Cox Regression)		
Variable	Log-rank test P-value	Unadjusted HR	95% CI	P value	Adjusted HR	95% CI	P value
History of Foker	0.132	1.61	(0.86 - 3.00)	0.136	1.6	(0.84 - 3.03)	0.151
History of Fundoplication	0.802	1.09	(0.53 – 2.22)	0.819			
Type of Fundoplication							
Full 360°	**0.015***	Reference	.	.	Reference	.	.
Partial		2.43	(1.16 - 5.11)	**0.019***	2.22	(1.01 - 4.78)	**0.045**
Mesh used	0.182	0.63	(0.33 - 1.24)	0.186	0.57	(0.25 - 1.31)	0.187
Location of Mesh							
Not used	0.36	Reference	.	.	Excluded due to collinearity with mesh used		
		0.41	(0.14 - 1.17)	*0.094*			
Anterior + Posterior							
Posterior		1.11	(0.34 - 3.62)	0.874			
Anterior		0.78	(0.3 - 2.02)	0.61			
MIS	0.064	1.87	(0.95 - 3.66)	*0.068*	2.57	(1.12 - 6.01)	**0.029**
Endoscopic Guidance	0.062	0.57	(0.31 - 1.04)	*0.065*	0.79	(0.39 - 1.57)	0.504

Univariate analyses were performed using the log-rank test and univariate Cox regression modeling.
Multivariable analyses were performed using multivariable Cox regression modeling.
HR = hazard ratio; CI = confidence interval; MIS = minimally invasive surgery.

Table 6
Lessons Learned Regarding Anti-Reflux Procedures in Complex EA Patients.

Modifications/Lessons Learned	Rationale/Alternative
1 Full 360-degree Nissen fundoplication should be performed whenever possible for complex EA patients who need an anti-reflux procedure.	Partial fundoplication was associated with greater risk of failure, and dysphagia was not different between partial and complete fundoplication.
2 Fundoplication via laparotomy should be given strong consideration.	A minimally invasive approach was associated with greater risk of fundoplication failure. Likely due to need for significant lysis of adhesions (most patients present with prior operations), technical challenges inherent with being able to perform the wrap above the GEJ, and the MIS approach creating fewer postoperative adhesions which could be beneficial at preventing ARP failure
3 Use of mesh-reinforcement may provide benefit in select instances.	The use of mesh to reinforce the hiatus and/or fundoplication itself was associated with a decrease ARP failure on univariate analysis. Further research is needed to confirm findings. Caution should be undertaken as mesh can cause erosion, for which long-term absorbable mesh products should be evaluated.
4 Endoscopy should be used to aid in locating the GEJ so that the fundoplication can be performed above the GEJ.	Complex EA patients often have asymmetric GEJ and prior scarring that can make it difficult to delineate the true location of the GEJ for which endoscopic guidance is very helpful.
5 In complex EA patients, ARP should be performed selectively in the setting of medically refractory GERD and not as routine practice.	ARP in complex EA patients carries significant morbidity and non-trivial failure rates. Every effort should be made to optimize anti-reflux medical therapy (PPI, H2B, prokinetic agents, post-pyloric feeding, etc.) prior to considering ARP.
6 ARP operative techniques or principles employed in non-EA or non-complex EA patients may not apply to complex EA patients.	Complex EA patients often have hiatal hernia, prior surgery, foreshortened esophagus, and small stomachs for which principles of minimal esophageal/hiatal dissection and few fundoplication stitches may not apply and may increase the risk of ARP failure, though further research is needed.

MIS – minimally invasive surgery, GEJ – gastroesophageal junction, ARP – anti-reflux procedure, EA – esophageal atresia. PPI= proton pumph inhibitor, H2B= Histamine receptor 2 blocker.

outcomes seen in this study with the MIS approach are related to less post-operative adhesions that would have been beneficial in these patients in preventing ARPF [35]. The MIS approach has been shown to have comparable results to its open counterpart while proving to be beneficial in terms of less pain, less wound morbidity and shorter hospital stay [35–37]. Some have shown that fewer wrap failures can be accomplished by decreasing the mediastinal dissection during a laparoscopic fundoplication. This was shown by Dr. St. Peter et al. in a randomized control trial and confirmed in a long-term follow up of this same population [38,39]. Although the evidence is compelling, the populations are vastly different. Our EA population is significantly more challenging (multiple prior operations, small stomachs, foreshortened esophagus, and greater proportion of LGEA patients) where even the presence of a hiatal hernia or an open operation excluded patients from this trial. Although an MIS approach has many benefits, these may not outweigh the risk of ARPF in patients with complex EA; hence, one must carefully consider these trade-offs. For example, given that the underlying etiology of medically refractory GERD tends to be different between an EA (e.g. hiatal hernia) and a non-EA patient (e.g. physiologic), it is conceivable that an ARP failure is more likely to present symptomatically (and require reoperation) in an EA patient; though further research should aim to elucidate this.

In some of our cases, we employed bovine pericardium mesh reinforcement as an onlay buttress to reinforce the crural repair and/or the wrap itself. Mesh has been advocated for use in adults with large hiatal hernias and risks factors for ARPF [40,41]. To our knowledge, only one small series of mesh reinforcement has been published in the pediatric population [42]. The study included 13 (non-EA) neurologically impaired children who underwent a fundoplication with mesh-reinforcement of the hiatus with good outcomes and the children experienced no *peri* or post-operative com-

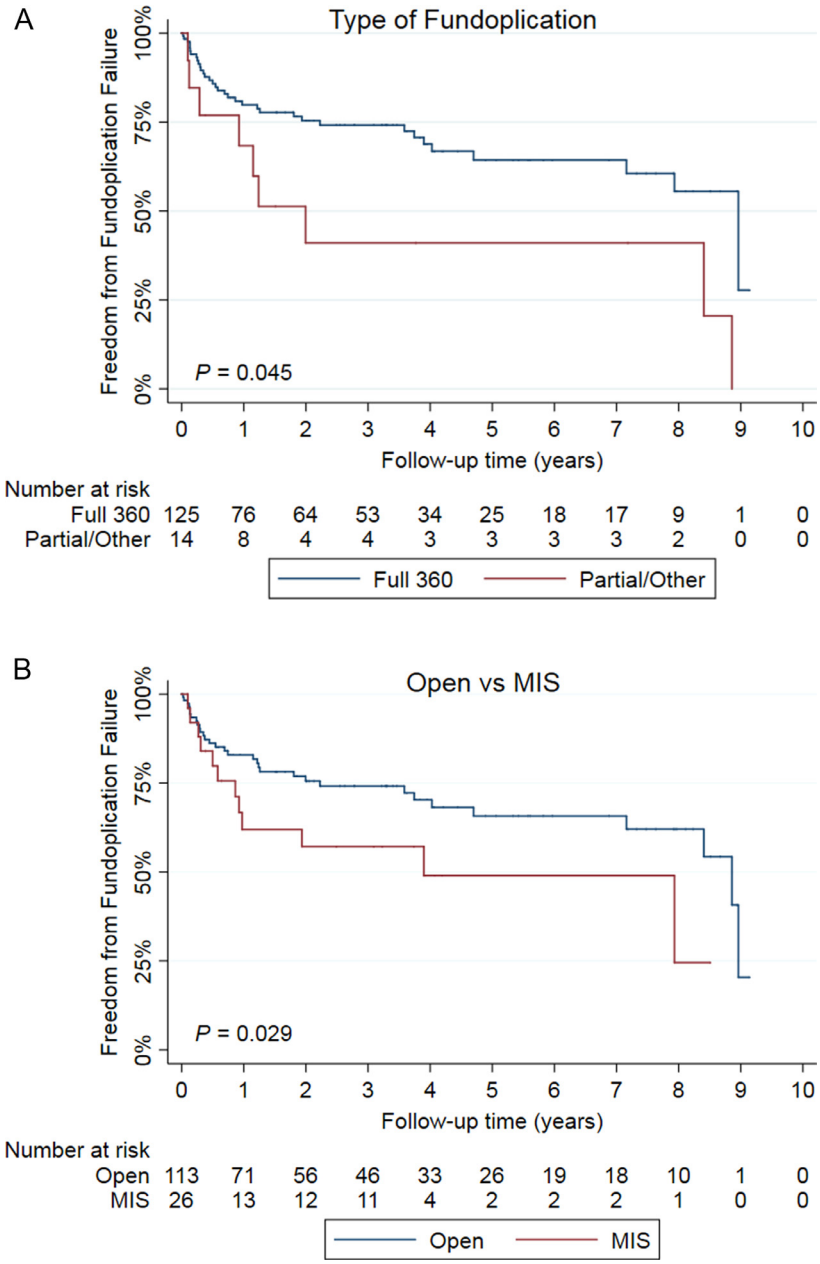

Fig. 3. 2a: Kaplan-Meier Curve comparing full 360° wrap vs partial wrap and time to wrap failure
2b: Kaplan-Meier Curve comparing open operative approach vs minimally invasive (MIS) approach for ARP and time to wrap failure. Includes only patients with full 360°-wrap.

plications. In our study, though the multivariable analysis did not reveal mesh to be a significant predictor of ARPF, the univariate analysis did with 39% failure in those without mesh compared to 21% failure in those who had mesh placed. We recognize the inherent risks with using mesh in this population; in fact, five of our patients experienced asymptomatic gastric erosions that were removed either endoscopically at the time of their surveillance endoscopy or at the time of the reoperation for ARPF. Mesh essentially works as a scaffold to enhance local tissue scarring; however, some mesh materials integrate better than others. Though we predominantly used permanent bovine pericardium mesh, newer long-term synthetic absorbable mesh products that integrate better and dissipate after a few years may hold promise in this area and warrant further study [43].

We recognize that our operative time was substantially longer than what has been previously reported. This is a challenging patient population and not only is the operative technique more involved, but our patients often present with multiple prior operations requiring significant lysis of adhesions. Our patients also require multiple associated procedures including diagnostic and therapeutic esophageal and airway endoscopies. In addition, challenging airways, vascular access and regional blocks all increase operative time. The reported operative time reflects the total time under anesthesia and included these additional procedures and safety measures implemented.

Over time, we noticed that the location of the endoscopically defined gastro-esophageal junction was often not the same as the one observed externally by the surgeon. We commonly see that EA patients, especially those with traction induced growth for LGEA, have an elevation of the GEJ and a distortion of the shape of the cardia and fundus of the stomach. In fact, the GEJ itself is often asymmetric with more elevation posteriorly compared to anteri-

orly, perhaps related to the difference in integrity of the phrenoesophageal ligament anterior versus posterior. We hypothesized that performing the wrap at the level of the endoscopic GEJ would lead to less risk of ARPF. Similar to mesh reinforcement, on multivariable analysis it did not prove to be a significant predictor of ARPF; however, the univariate analysis, showing a 22% failure rate in those with endoscopic guidance compared to a 48% failure in those without, make it an intriguing factor to consider and an area that merits further study. We think that such endoscopic GEJ identification is particularly useful for cases in which prior surgery and scarring may obscure the external boundaries of the GEJ. Endoscopy is also crucial at the time of the fundoplication in this patient population as it evaluates for the presence and severity of co-existing esophageal pathology, such as esophagitis and/or an esophageal anastomotic stricture. We certainly do advocate for endoscopy to assist with ARP in this patient population.

Practice patterns have evolved over time in our institution. We have changed from performing a fundoplication on all EA patients having undergone a Foker procedure to selectively deciding in whom and when we perform an ARP. Several factors have likely contributed to this. The efficacy, safety profile and widespread availability of anti-acid medications and other pharmacological agents have flourished in recent years [44]. As use of anti-acid therapy increases, especially the use of histamine blockers, additional points of morbidity will need to be evaluated including rate of SSI's, or other known complications related to pharmacologic therapy. Similarly, the availability, experience and comfort with managing post-pyloric feeding tubes in this patient population has allowed us to reserve the ARP for those who truly fail medical management [45,46].

4.1. Limitations

Our study has several limitations that we acknowledge. Our referral practice does not truly represent the typical patient with EA. Our patient population is comprised of patients on the more severe end of the EA spectrum, often with multiple prior operations. Nearly half of our cohort were patients with a prior Foker procedure for long-gap esophageal atresia. Hence, our results may not be applicable to other centers. Our data was also collected retrospectively and thus is prone to the inherent biases associated with chart review, data collection and patients lost to follow-up. Within our groups, there are limitations due to apparent heterogeneity. Two examples of this include within the MIS group and the partial fundoplication group. The MIS group consists of both standard laparoscopic and robotic approaches which may result in different outcomes. The comparison between partial and complete type fundoplication is at risk for bias. The partial fundoplication group was small and heterogeneous and thus may not accurately represent the outcome of each individual type of partial fundoplication. Additionally, further research is needed to determine a consistent definition of success following ARP that encompasses the many indications. Individual surgeon preference was difficult to account for and may have contributed to selection bias with decisions such as operative approach, use of mesh, partial vs. complete fundoplication, performance of pyloroplasty, and/or endoscopic guidance.

4.2. Conclusion

Our study highlights the following key findings: 1) Anti-reflux procedures in patients with complex esophageal atresia are challenging and can result in a significant rate of failure. Though our study does not particularly address a volume-outcome relationship, given the rarity of this condition and the challenges associated with these patients, we believe they should be cared for in centers with experience treating complex EA patients. 2) In our practice, a full 360-degree Nissen fundoplication via an open approach provides the least risk for anti-reflux procedure failure. 3) Mesh reinforcement and endoscopic guidance appear to decrease the risk for failure but warrant further study. One must be cautious of the potential for mesh-erosion, and novel long-term absorbable synthetic mesh products should be studied.

Previous communication

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