GER in EA-TEF

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of Patients
Patient characteristics</th><th>Classification Types and Survival Rates</th><th>GER</th><th>Strictures</th><th>Respiratory</th><th>Conclusion</th></tr>
<tr>
<td>Konkin et al
2003 (1)</td>
<td>Retrospective review of charts between 1984-2000</td>
<td>144
87M, 57F
Mean gestational age 37wk(27-42)
Average birth weight 2485g (745-4599)

EA Types
Type A 13 (9%)
Type B 2 (1%)
Type C 119 (83%)
Type D 2 (1%)
Type E 8 (6%)

Associated anomalies 74 (51%)
Of these Gastrointestinal 23%

140 underwent operative repair Survival rate 95%

100 had primary repair
35 had 2 stage repair

Post op complications:
Anastomotic leakage 8%
Recurrent fistula 8%

12 deaths (Overall Mortality rate 8%)</td>
<td>
<table>
<tr><th>Criteria</th><th>Published Survival rate</th><th>Our number</th><th>Our Survival rate</th></tr>
<tr><td>Waterston</td><td></td><td></td><td></td></tr>
<tr><td>A</td><td>95%</td><td>39</td><td>100%</td></tr>
<tr><td>B</td><td>68%</td><td>46</td><td>100%</td></tr>
<tr><td>C</td><td>6%</td><td>59</td><td>80%</td></tr>
<tr><td>Montreal</td><td></td><td></td><td></td></tr>
<tr><td>I</td><td>93%</td><td>79</td><td>92%</td></tr>
<tr><td>II</td><td>31%</td><td>7</td><td>71%</td></tr>
<tr><td>Spitz</td><td></td><td></td><td></td></tr>
<tr><td>I</td><td>97%</td><td>93</td><td>99%</td></tr>
<tr><td>II</td><td>59%</td><td>44</td><td>84%</td></tr>
<tr><td>III</td><td>22%</td><td>7</td><td>43%</td></tr>
<tr><td>Bremen</td><td></td><td></td><td></td></tr>
<tr><td>Without complication</td><td></td><td></td><td></td></tr>
<tr><td>I</td><td>100%</td><td>48</td><td>98%</td></tr>
<tr><td>II</td><td>50%</td><td>14</td><td>86%</td></tr>
<tr><td>III</td><td>0%</td><td>1</td><td>100%</td></tr>
<tr><td>With complication</td><td></td><td></td><td></td></tr>
<tr><td>I</td><td>33%</td><td>7</td><td>100%</td></tr>
<tr><td>II</td><td>40%</td><td>12</td><td>83%</td></tr>
<tr><td>III</td><td>0%</td><td>4</td><td>25%</td></tr>
</table>
Survival rate for Montreal I (92%) was greater than II (71%), but not significant (p=.08)
There was a statistically significant difference between Spitz type I (99%), II (84%) and III (43%), P<.05
Insufficient numbers for statistical analysis between groups I, II and II (100%, 83% and 25% respectively) of Bremen without classification
No difference in Bremen classification without complications, group 1 (98%), group 2 (86%) and 100% for group 3.
</td>
<td>GER 31%

17 (12%) had fundoplication
16 pre 1992
1 post 1992</td>
<td>Definition:
Any narrowing seen in contrast study which was dilated at least once Stricture

Stricture rate 52%</td>
<td>Pneumonia 6%</td>
<td>BW was not a significant factor for mortality

Congenital anomalies were not strong predictors for survival

Stricture rates are high

Low fundoplication rate in second half of study period due to liberal use of PPI/H2 blockers

Spitz classification system is able to best predict prognosis for patients with EA-TEF</td>
</tr>
</table>

GER in EA-TEF

Author/Year	Study Type	Number of patients Patient characteristics	Indications for fundoplication	Pre-operative investigations	Type of fundoplication	Post-operative complications	Follow up Post-operative investigations	Conclusion
Esposito et al 2005 (2)	Retrospective study Between 1998-2002 4 centers	21 EA patients 14M, 7F Median age at surgery 26months (6mths-8yrs) Median weight 9.1kgs (4-23Kgs) 5 (23.8%) were neurologically impaired children (NIC) 1 VACTERL 1 Previous Aortopexy	GER + Aspiration 100% Esophagitis + peptic stricture 5 (23.8%) Feeding difficulties 5 (23.8%) 2 (9.5%) Redo fundoplication for recurrence of GER Persistent symptoms on PPI 100%	pH Metry 100% Barium swallow 100% Endoscopy 15 (71%) BAL 7 (33.3%) Scintigraphy 9 (42%) Manometry 5 (23.8%)	Neurologically normal children Toupet 3 (18.7%) Thal 7 (43.7%) Nissen 6 (37.7%) Gastrostomy done in all NIC Median hospital stay 3days (2-9)	No intra-operative complications No mortality **Neurologically normal** 100% free of symptoms Normal oral intake None have gas bloat syndrome Not on any anti reflux medications 5 (31.2%) had mild dysphagia which resolved in 3-6mths 100% can burp 11 (68.7%) can vomit No significant difference between type of surgery and ability to vomit (P=NS) No significant difference between type of surgery and incidence of dysphagia (P=NS) 1 pt. had aspiration 2yrs post surgery although barium and pH metry were normal	Median F/U 24mths (12mths-6yrs) All had pH metry and Barium swallow at maximum of 6 yrs. post op	All 3 procedures: Nissen, Thal and Toupet achieved comparably good results Mild Dysphagia seen in 31.2% of neurologically normal children which resolved over time., and there was no significant difference between type of fundoplication and incidence of dysphagia Esophageal dysmotility may cause regurgitation, aspiration and respiratory problems post fundoplication even if GER was well controlled by anti reflux procedure Prokinetics might have a role in treating esophageal dysmotility Results of preoperative and post-operative investigations not given in detail

						NIC 4 are on gastrostomy + oral feeds 1 only has gastrostomy feeds 2 still have respiratory symptoms 1 has delayed gastric emptying and is on prokinetics		

GER in EA-TEF

Author/Year	Study Type	Number of patients Patient characteristics	Gastrointestinal symptoms Dysphagia/Stricture/GER	Growth/Nutrition	Lifestyle	Conclusion
Chetcuti et al 1988 (3)	Retrospective review	Between 1948-1968 248 EA patients 145 survived to 18yrs 125 (107 attended review and 18 had a telephone interview) In total 86% of survivors were reviewed Mean age 25 years Oldest person was 39 68M, 57F EA Types Type A 5 (3 primary anastomosis, 2 esophageal replacement) Type C 134 (133 primary anastomosis, 1 esophageal replacement) Type E 6 Post-operative complications Anastomotic leak 26 (18.7%) Recurrent Fistula 10 (7.1%)	Anastomotic stricture 76 (54.7%) Dysphagia was more common in patients who had a stricture ($p<.05$) No relationship between GER and dysphagia Dysphagia Occasional 67 (53%) Daily 16 (13%) GER Heartburn Occasional 57 (46%) >once/week 14 (11%)	Weight <3rd centile 3 (2.4%) 3-25th centile 22 (17.6%) 25-75th centile 59 (47.2%) 75-97th centile 18 (14.4%) >97th centile 4 (3.2%) Height <3rd centile 1 (0.8%) 3-25th centile 18 (14.4%) 25-75th centile 72 (57.6%) 75-97th centile 15 (12%) >97th centile 15 (12%)	81 (65%) had hospitalisations for GI problems in first 10years. None had lost more than 10days in preceding year for GI problems	Over half had daily gastrointestinal symptoms; none regarded these as having significant impact on life. Dysphagia was present in over half the adults, but most enjoyed a normal diet and seldom required medical attention.

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of patients
Patient characteristics</th><th>Symptom Questionnaire Results
Dysphagia/GER</th><th>Endoscopy</th><th>Conclusion</th></tr>
<tr>
<td>Deurloo et al
2003 (4)</td>
<td>Prospective analysis

Study on the prevalence of GER and its complications in adults</td>
<td>40 patients
Who had EA repaired between 1947-1972

26M, 14F
Mean birth weight 2760g (1960-3600)
Mean gestational age 39weeks (34-42)
9 (23%) had associated congenital malformations

EA Types
39 Type C
1 Type A (long gap)

Primary repair 38
Colon interposition 2

None were on anti reflux medications
1 had Boerema anterior gastropexy (anti reflux procedure)

16 (40%) >3 dilatations
(not clear whether dilatations were for symptoms/stricture/or routine)</td>
<td>Questionnaire completed by 38 (95%)
Mean age of responders 34yrs (28-45)

10 (26%) asymptomatic

Dysphagia

13 (34%) Dysphagia with solid food
2 (5%) Dysphagia with mashed food
4(11%) had limitations to type of food
15 (40%) needed to wash down food with drinks
Most common food-meat/rice

Recurrent respiratory problems 5 (13%)

GER

Heartburn 7 (18%)
Retrosternal pain 8 (21%)
Both 5 (13%)</td>
<td>23 (61%) had endoscopy (EGS)
No difference in number of patients who had endoscopy between those with complaints 17/28 vs those without complaints 6/10, p=NS

EGS

Macroscopic appearance
Normal 19 (82%)
Grade I esophagitis 2 (9%)
Barrett’s (Grade V) 2 (9%)

Hiatal hernia 13
Patients with hiatal hernia did not have more complaints, worse findings on EGS and histology

Histology

Biopsies taken in 21/23
Normal 1 (5%)
Mild esophagitis 8 (38%)
Moderate esophagitis 8 (38%)
Severe esophagitis 3 (14%)
Intestinal metaplasia 1 (5%)
(1/2 with macroscopic Barrett’s had IM)

<table>
<tr><th>Histology</th><th>Normal</th><th>Grade I</th><th>Barrett</th><th>Total</th></tr>
<tr><td>Normal</td><td>1</td><td>0</td><td>0</td><td>1</td></tr>
<tr><td>Mild Esophagitis</td><td>8</td><td>0</td><td>0</td><td>8</td></tr>
<tr><td>Moderate Esophagitis</td><td>6</td><td>1</td><td>1</td><td>8</td></tr>
<tr><td>Severe Esophagitis</td><td>2</td><td>1</td><td>0</td><td>3</td></tr>
<tr><td>Intestinal Metaplasia</td><td>0</td><td>0</td><td>1</td><td>1</td></tr>
<tr><td>No Biopsies</td><td>2</td><td>0</td><td>0</td><td>2</td></tr>
<tr><td>Total</td><td>19</td><td>2</td><td>2</td><td>23</td></tr>
</table>

No correlation between complaints/macroscopic findings/histology

Patient who had gastropexy had normal EGS and biopsy

1 (5%) developed dysphagia subsequently and was diagnosed with Squamous Cell carcinoma (T3N0M0)
Transthoracic subtotal esophagectomy with gastric tube interposition done. No recurrence after 3 yrs</td>
<td>One of first studies to look at prevalence of GER in adults with questionnaire, EGs and histology

Three quarters of patients had complaints which did not affect daily activities

A third had dysphagia with solids

Although not all patients had EGS, even if those who did not have it were hypothetically categorized as having normal histology, the prevalence of histologically proven abnormalities would still be 63% (24/38)

Study found I case of SCC

Study showed high prevalence of esophagitis due to chronic GER and a high frequency of complications, but no correlation between subjective and objective findings

? Role for regular surveillance EGS with biopsy in adult EA survivors</td>
</tr>
</table>

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient characteristics	Co morbidities	Recurrent TEF	Tracheomalacia Aortopexy	Stricture Dilatations	GER	Anti reflux surgery (ARS)	Growth Nutrition	Conclusion
Deurloo et al 2002 (5)	Retrospective review From between 1947-2000	371 EA patients 215 (58%) M 155 (42%) F 1 ambiguous genitalia 269 survivors Mean BW 2552g (650-4160) 32 (9%) had BW<1500g Mean gestational age 38wk (26-43) 114 (31%) were premature Over 5 time periods 1947-1968 1994-2000 the mean BW decreased (p=NS) and mean gestational age also decreased from 39 to 37 wks. (p=.01) EA Types Type A 25 (6.7%) Type B 2 (0.5%) Type C 329 (88.7%) Type D 2 (0.5%) Type E 13 (3.5%)	175 (47%) had other congenital anomalies Duodenal Atresia 18 (4.9%) Pyloric stenosis developed in 16/288 (5.5%) evaluable patients 14 had Type C 2 had Type A	7(2%) 5 had Type C, EA 2 had type A, EA No correlation between anastomotic tension or pleural lesion and recurrent fistula	Clinically significant tracheomalacia in 34/269 (13%) Based on symptoms and tracheobronchoscopy Aortopexy 18/34 (53%) 13/18 (72%) also had ARS Since 1986 ARS always done before aortopexy Pre 1986 patients had aortopexy first but numbers too small to assess statistical significance 9/16 vs 9/21, p=.42 Patients with GER more often had tracheomalacia 25/87 vs 9/182, p<.0001	An anastomotic stricture requiring >3 dilatations in 47/269 (17%) GER diagnosed in 22 (47%) of these patients 14 /22 (64%) of these patients had subsequent anti reflux surgery (ARS)	**pH metry** Done in 120/269 survivors (45%) GER seen in 48/120 (40%) Since 1986 patients were routinely screened for GER with pH metry 3 months after EA repair Results of pH Metry post 1986 1947-1985 37/150 (25%) 1986-2000 53/128 (41%) GER diagnosed based on symptoms or pH metry in 87/269 (32%) GER seen more in Type A and Type B with Long Gap 9/14 (62%) than in other types 78/255 (30.5%), p<.05 No correlation between GER and anastomotic tension or pleural lesion during operation Recurrent respiratory problems occurred in 87/269 (32%) Patients with GER more often had recurrent respiratory problems 45/87 vs 42/182, p<.0001	A Boerema anterior gastropexy was the standard anti reflux surgery (ARS) done ARS done in 61/269 (23%) **Indication for ARS** Failure of maximal conservative therapy for GER in 58/61 (95%) ALTE 2/61 (3.2%) Redo ARS in 7 (11%) 3 also had Nissen fundoplication with anterior gastropexy	Growth normal in 250/269 (93%) with height and weight above 5th centile Height and weight were below 5th centile in 19/269 (7%) Patients with GER more often had impaired growth 13/87 vs 6/182, p<.005 Patients with BW <1500g more often had impaired growth 6/17 vs 13/252, p<.0005 No correlation between type of atresia and impaired growth	In recent years EA patients are born earlier, weigh less and have more associated anomalies than those treated 50 years ago. Increased incidence of pyloric stenosis (6% of all EA and 13% of Type A EA) compared to normal population (0.1-1%)? this is due to vagal lesion, gastrostomy and trans pyloric feeding tubes Clinically significant tracheomalacia can be aggravated by GER and eradication of GER was done prior to aortopexy. Routine screening for GER since 1986 has increased the number diagnosed with GER (42%) Treatment of GER has also been more aggressive post 1986 with more ARS , from 15% to 32% Consequently the number of patients requiring multiple dilatations for anastomotic stricture has decreased from 10% pre 1985 to 2% post 1985, p=.01

										Failure rate for Boerema anterior gastropexy was 11%, which is lower than the failure rate of Nissen or Thal fundoplication (15% to 30%)

GER in EA-TEF

Author/Year	Study Type	Number of patients Patient characteristics	Indications for Fundoplication	Complications post Fundoplication	Investigations	Conclusions
Curci et al 1988 (6)	Retrospective review Between 1975-1986	36 EA patients 14 (45%) had fundoplication GER treatment included: Thickened feeds Elevation of patient in prone position Metoclopramide H2 Blockers 8 had fundoplication during initial hospitalization (6wk-5.5mths) Gestational age and weight were equally distributed amongst patients having fundoplication	Majority of patients weighing <2000g with EA had refractory GER which required surgery Indications for surgery: Failure to thrive 7 (50%) Recurrent aspiration and/or apnea 8 (57%) Anastomotic stricture 2 (14%) Several had >1 indication	Dysphagia (for formula) 7 (50%) These children required gastrostomy supplementation In 5/14 (36%) dysphagia persisted beyond 12 months post surgery	4/7 with dysphagia had manometry and pH metry All (100%) had normal LESP (>15mmHg) All (100%) had normal pH metry All had absent peristalsis distal to anastomosis Length of intra-abdominal portion of LES <1cm	36% of patients had dysphagia lasting >1yr post fundoplication in this study. Authors concluded that preoperative manometry and pH metry are needed to evaluate LESP and esophageal motility. If LESP is low/normal and only minor abnormalities in esophageal motility fundoplication might be appropriate. If major dysmotility is present caution to be used when deciding on need for fundoplication. Gastrostomy feeds might be needed if there is prolonged dysphagia A subsequent EA patient with anastomotic stricture was therefore investigated with manometry which showed normal LESP and pH metry which showed normal acid clearance, as both anti reflux mechanisms were intact fundoplication was deferred and dilatation of stricture was done. Limitations of study: There was no comment on whether the LESP was high No comment on whether there was adequate relaxation of LES with swallows or whether there was hold up PPIs were not used to treat GER in this study, which might be a reason for the high fundoplication rate

GER in EA-TEF

Author/Year	Study Type	Number of patients Patient characteristics	Indications for Total Esophagogastric Disassociation (TED)	Outcomes/Complications of TED	Conclusion
Laguasie et al 2005 (7)	Retrospective review Between 1999-2003	13 TEDs done 6M, 7F Mean age 35 months (14 days-218months) 9/13 (69%0 were EA patients 7 with coloplasty 2 with native esophagus Type C 6 3/6 had esocoloplasty 2 had previous fundoplications (3&4 previous ones) 1 had associated Type II Tracheoesophageal cleft (2 previous failed attempts at repair Type A 3 TED done at time of esocoloplasty	Severe persistent reflux 6 had previous failed fundoplications (1-4) Failed repair of tracheoesophageal cleft	Average F/U 26mths (1-4yrs) 3 died at 3/4/12mths from acute respiratory failure Amongst survivors 10 2 (20%) have ongoing respiratory disorders ½ is an EA patient Gastrostomy removed in 2 (18 and 24mths) Post removal F/U of 6 and 24 mths 1 only gastrostomy fed Other 8 have discontinuous feeds via gastrostomy (100-900mls/day) Chronic diarrhea 2 which improved with dietary measures 7 have achieved functionally normal oral feeds of limited amounts Esojejunal stricture in 1-dilated Mean F/U weight is 0.5SD below average (-1.5-+0.5 SD)	Severe GER in some EA patients especially those with esocoloplasty may require TED TED is only indicated when lung function is damaged by severe GER or when surgery for tracheoesophageal cleft has failed TED helps with reflux control and GER associated swallowing disorders, recurring respiratory infections and failure to thrive Long term F/U is needed to evaluate the Roux En Y esophagojejunal anastomosis and its impact on feedings When long gap EA require esophagcoloplasty, authors do TED at the same time to reduce risk of feed stagnation in colonic graft leading to aspiration and recurrent pneumonitis Authors feel TED should not be done on a rescue basis but earlier as a primary preventative measure before chronic respiratory failure TED has no effect on swallowing disorders not secondary to GER Gastrostomy should be maintained for at least a year for endoscopic and functional evaluation of disconnected stomach Early post op period feeds are mainly via gastrostomy but with swallowing acquisition and coordination oral feeds are achieved Diarrhea post TED could be due to Dumping. Hence pyloroplasty should be avoided Esocolic anastomotic stricture could be due to reflux of small bowel secretions, hence regular endoscopic F/U is needed

GER in EA-TEF

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of Patients
Patient Characteristics</th><th>Symptoms</th><th>Endoscopy</th><th>pH Monitoring</th><th>Conclusion</th></tr>
<tr>
<td>Castilloux et al
2010 (8)</td>
<td>Prospective cross sectional Study
From 2005-2008</td>
<td>76 patients
Patients with gastric tube reconstruction, Bianchi, colonic interposition were excluded

All EA patients >4yrs and symptomatic (dysphagia, food impaction, hematemesis) patients <2yrs were offered endoscopy

63 Underwent endoscopy
18 had strictures which needed dilatation, these were excluded as no biopsies were taken

Final number 45
26F
Median age 7.3yrs (5mths-17yrs 11 mths)
EA Type C 37 (82%)
Long Gap (LG) 10 (22%)
VACTERL 11 (24%)
Fundoplication 20 (44%)
Prior Stricture needing dilatation 10 (22%)</td>
<td>28 (62%) were symptomatic
Dysphagia 40%
Food impaction 36%
Coughing during meals 27%
Regurgitation 20%
Pyrosis 13%
Odynophagia 2%</td>
<td>Macroscopic esophagitis classified according to Savary Miller
Esophagitis defined by presence of pappilary elongation and basal hyperplasia
Barrett Esophagus (BE) classified as per Montreal classification as GM+ or IM+
Endoscopy considered normal if no evidence of macroscopic or microscopic esophagitis, no BE/GM+ or BE/IM+

26 (58%) had normal endoscopy
14 (31%) has histologically proven esophagitis
16 (36%) had BE /GM+
In this group mean age was 9.8yrs (3.4-13.2) and 6 had LG
No BE/IM+ /dysplasia or adenocarcinoma was seen
Both esophagitis and GM were seen in pts >4yrs

Of 17 asymptomatic patients 6 had abnormal endoscopy
4/6 had esophagitis and GM
Of 28 symptomatic patients 15 had normal endoscopy

No association seen between symptoms and endoscopy findings analysed either as whole (abnormal endoscopy) or separately (esophagitis or GM)
<table>
<tr><th></th><th>Normal Endoscopy N=26</th><th>Abnormal Endoscopy N=19</th></tr>
<tr><td>Regurgitation/GER</td><td>4 (%)</td><td>5 (26%)</td></tr>
<tr><td>Pyrosis</td><td>2 (8%)</td><td>4 (21%)</td></tr>
<tr><td>Dysphagia</td><td>10 (38%)</td><td>8 (42%)</td></tr>
<tr><td>Odynophagia</td><td>1 (4%)</td><td>0 (0)</td></tr>
<tr><td>Food Impaction</td><td>10 (38%)</td><td>6 (32%)</td></tr>
<tr><td>Cough at meals</td><td>6 (23%)</td><td>6 (32%)</td></tr>
<tr><td>Asymptomatic</td><td>11 (42%)</td><td>6 (32%)</td></tr>
</table>
</td>
<td><1yr Reflux Index >10%
>1yr Reflux Index >5%
was considered abnormal

Done in 24/63

Out of 14 pts with esophagitis, 6 had pH metry and was abnormal in all not on meds

Of 16 patients with BE/GM+ 7 had pH metry and was abnormal in 3/7</td>
<td>Abnormal endoscopy in (42%)
Symptoms in 62%

No symptom was statistically associated with abnormal endoscopy

6 asymptomatic patients also had abnormal endoscopy

If patients with strictures had been included in analysis, dysphagia would have been statistically associated with abnormal endoscopic finding of stricture requiring dilatation

5 patients with GM have had subsequent endoscopy with no IM+ seen

However total number of biopsies taken did not follow guidelines for BE surveillance, so some GM and IM could have been missed and study might be underestimating true number of GM and IM

Lack of association between symptoms and endoscopy could have been because of small sample size

Symptoms not predictive of abnormal endoscopy in EA patients. Esophagitis and GM can be seen in absence of symptoms. Physicians cannot rely solely on symptomatology to accurately evaluate extent of esophageal complications in this population.</td>
</tr>
</table>

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Results of Electrogastrography (EGG)	Conclusion
Cheng et al 1997 (9)	Prospective case control study	18 EA patients 18 were Type C and had primary repair 2 Type A had staged repair with initial cervical esophagostomy and feeding gastrostomy Mean age of EApts 2.3yrs (2wks-12yrs) 3/18 patients had symptomatic GER 10 normal controls Mean age 2.1yrs (1mth-10yrs)	The means of the dominant frequencies and the ranges of the frequency distribution in EGG in the two groups were compared EGGs done 1week to 12 years following repair EA 2 patients had bradygastria 2 patients had tachygastria These 4 did not have GER symptoms The means of the dominant frequencies in the EA and control groups did not differ significantly (P>.1) EA group had a wider frequency distribution than the control group. (P=. 002) The range was twice than that of controls. This difference was significant in channels 2 and 3 where the electrodes are over the gastric antrum. The difference was not significant in channel 4 and close to being significant in channel 1. There was a tendency for wider frequency distribution in the post prandial phase in channels 1 and 2 When reflux and non-reflux patients were compared in the EA group, the former had a wider EGG frequency span in 3 out of 4 channels, but only 1 was statistically significant	The wider frequency distribution of EGG in EA patients suggests disturbed electrical activity of the stomach, which could be associated with poor electromechanical coupling and abnormal gastric contraction. The wide EGG frequency distribution implies the gastric pacemaker is not pacing a regular rhythm or the activity of the smooth muscle cells is affected due to abnormal myenteric plexus seen in EA patients resulting in incoordination gastric contraction and delayed gastric emptymg Tachygastria and bradygastria were seen in EA and dysrrthythmias and tachygastria are known to be associated with nausea and delayed gastric emptying LOW GER rate could be due to EGG being done soon after EA repair and short follow up.

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Symptoms	pH Metry	Gastric Scintiscan	Analysis of correlations between factors assessed for prognostic relevance	Conclusion
Jolley et al 1980 (10)	Case series	25 patients 62 EA patients were considered 6 with prior fundoplication were excluded Of remaining 56, 25 consented 17M, 8F 3-83months post repair All Type C 9 had high proximal pouch 16 had low proximal pouch 8 had gastrostomy 0 recurrent fistula 7 had small anastomotic leak 11 had strictures requiring 2 or more dilatations	Symptoms evaluated in 6 months prior to study 7 had vomiting 1 had growth retardation due to vomiting/esophagitis 10 had aspiration pneumonia/apnea/choking 6 had more than 1 symptom Symptomatic children were more likely to have GER and sloe gastric emptying 10/12 (83%) with symptoms had significant GER Incidence of GER was unaffected by type of symptoms Vomiting 86% Respiratory 80% Associated major disorders 73% A large portion of asymptomatic children also had GER 3/10 (30%) symptomatic children with GER had subsequent fundoplication due to failure of medical therapy (1-aspiration, 1-apnea, 1-growth retardation and esophagitis)	All had pH Metry pH score >64=significant GER Classification Type I Continuous Type II Discontinuous Type III Mixed Classification done by analyzing distribution of reflux episodes in 14 consecutive 15min intervals after feeding apple juice 17 (68%) had significant GER GER Patterns Discontinuous pattern in 11/17 (65%) and was associated with slow gastric emptying 13/17 (77%) had a decrease In frequency of GER between 2-3hours post prandially (Type II and III) Gastric emptying was slow in Type II and III compared to type I and normal Of 11 patients with Type II, 6 were >1yr old Incidence of Type ! In EA (23%) was less than that in normal (48%)	20 (80%) had scintiscan 13/20 (65%) had significant GER on scintiscan Gastric emptying was slower in patients with GER on scintiscan, p<. 005 Degree of gastric emptying was unrelated to degree of GER as measured by reflux index, P=NS	Excessive tension at esophageal anastomosis was the only factor subsequently associated with a high incidence of GER (88% vs. 59%)and slow gastric emptying (11.2+/- 4.2% vs. 25.9 +/- 3.7%), p<. 05 The trend towards higher incidence of GER and slow gastric emptying in children with a leak or stricture resulted from the association of the two post-operative complications with anastomotic tension Only 1/3 patients with anastomotic stricture but without tension or leak had GER Neither patients with congenital lower esophageal stenosis had GER or esophagitis	Significant GER is not universal following repair of EA-TEF, it occurred in 2/3rds of patients in this study It is of the Type II or III pattern, which is associated with slow gastric emptying and tension leak or stricture at anastomotic site. Only 30% of symptomatic children required fundoplication to control symptoms. Type II pattern is rarely seen in >10mths age but was seen in EA pts. as old as 5yrs which suggests that they may have chronic impairment of gastric emptying

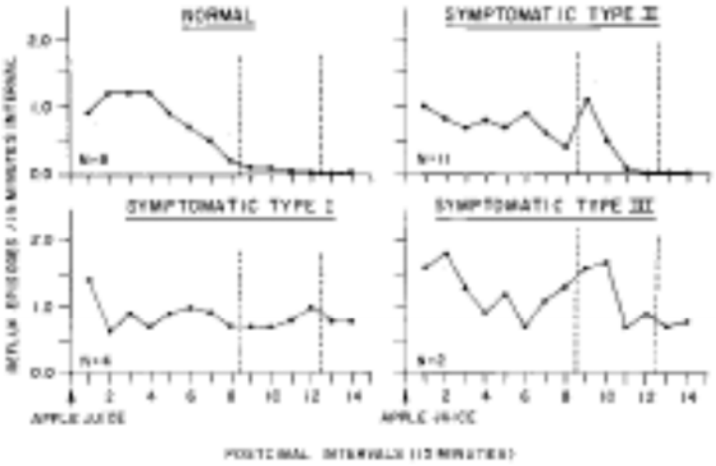

Fig. 2. Patterns of gastroesophageal reflux (GER) following the ingestion of apple juice (300 ml/m² BSA) by 25 children with repaired esophageal atresia and distal tracheoesophageal fistula.

<table>
<tr><th>Author/Year</th><th>Type of Study</th><th>Number of Patients
Patient Characteristics</th><th>Gastrostomy</th><th>Conclusion</th></tr>
<tr>
<td>Black et al
1991 (11)</td>
<td>Retrospective Review</td>
<td>116 EA patients studied in 2 centers (LBCMC and CFWCH)
Distribution of infants was similar
<table>
<tr><th></th><th>LBCMC
54</th><th>CFWCH
62</th></tr>
<tr><td>Type A</td><td>3 (5.6%)</td><td>5 (8.1%)</td></tr>
<tr><td>Type C</td><td>48 (88.9%)</td><td>51 (82.3%)</td></tr>
<tr><td>Type D</td><td>1 (1.9%)</td><td>2 (3.2%)</td></tr>
<tr><td>Type E</td><td>2 (3.7%)</td><td>4 (6.5%)</td></tr>
<tr><td>Other anomalies</td><td>70.4%</td><td>56.5%</td></tr>
<tr><td>GI Anomalies</td><td>14 (25.9%)</td><td>6 (9.7%)</td></tr>
</table>
Distribution of patients according to their mortality and Waterston classification was similar</td>
<td>80 had gastrostomy, 66 early survivors
32 had primary repair of EA without gastrostomy
<table>
<tr><th></th><th>LBCMC
54</th><th>CFWCH
58</th><th>Early Survivors</th></tr>
<tr><td>Gastrostomy</td><td>51
(94.4%)</td><td>29
(50%)</td><td>66</td></tr>
<tr><td>No Gastrostomy</td><td>3
(5.6%)</td><td>29
(50%)</td><td>31</td></tr>
</table>
Of 97 surviving infants 65 had UGI
(66% at LBCMC and 68% at CFWCH)
In gastrostomy group 30 (45.5%) had GER by UGI and 12 had subsequent fundoplication
In those without gastrostomy, 11 had GER and 4 had fundoplication
<table>
<tr><th></th><th>LBCMC</th><th>CFWCH</th></tr>
<tr><td>Gastrostomy</td><td></td><td></td></tr>
<tr><td>GER+</td><td>20/44
(45.5%)</td><td>10/22
(45.5%)</td></tr>
<tr><td>Fundoplication</td><td>7/44
(15.9%)</td><td>5/22
(22.7%)</td></tr>
<tr><td>No Gastrostomy</td><td></td><td></td></tr>
<tr><td>GER+</td><td>0/3</td><td>11/28
(39.3%)</td></tr>
<tr><td>Fundoplication</td><td>0/3</td><td>4/28
(14.3%)</td></tr>
</table>
There was no significant difference in incidence of GER between those with and without gastrostomy

There was no significant difference between patients with or without gastrostomy who subsequently required a fundoplication</td>
<td>This data suggests gastrostomy does not significantly contribute to GER or need for fundoplication in EA-TEF

The fact that gastrostomy does not contribute to GER in EA suggests an intrinsic etiology for GER (congenital or acquired)</td>
</tr>
</table>

GER in EA-TEF

Author/Year	Type of Study	Number of Patients Patient Characteristics	Survival	Respiratory	Stricture	GER	Conclusion
Bouguermouth et al 2014 (12)	Retrospective Review Between 2001-2011	86 12 excluded (9 died and 3 were Type E) 46M, 42F EA Types Type A 12 (14%) Type B 2 (2%) Type C 58 (67%) Type D 2 (2%) Type E 3 93%) Associated anomalies 52 (60%) GI 9 (10%) Right aortic arch 3 (4%) Follow up 3mths-10yrs Long Gap >3cms 13 (17%) Mean age at esophageal substitution 7mths Average gestational age 36+/0 2 Average birth weight 2300+/-570g Average age at admission 3days (1-35) Feeding prior to repair 36/74 (48%) Surgery done 5days after birth (1-37) Contrast done post repair on 5-7days post surgery	45/74 (60.8%) Factors affecting post op survival Age at time of admission p=.028 delay >48hrs before babies reached hospital (56.7%) Prematurity P=.024 Long gap P=.01 P=NS Feeding prior to repair Weight Associated anomalies Place of delivery History of feeding Anastomotic leak Primay/delayed/esophageal substitution Waterston classification	Bronchoscopy done at 3 months post repair in symptomatic babies Tracheomalacia/Broncho pulmonary infections 24/45 (53%) Recurrent TEF 3/45 (7%) Mean time for recurrence was 15mths (3-24)	Stricture 26/45 (58%) 5 dilatations per patient (1-10) Bougie used Started 4 weeks post op and repeated every 1-3weeks until stable diameter reached	Routine scope done at 1 month post repair to look for stricture/esophagitis GER 22/45 (49%) A of GER had fundoplication	GER rate of 49% and a third needed fundoplication Poor outcome (60.8% survival rate) related to delayed diagnosis, LBW and lack of advanced neonatal management

GER in EA-TEF

Author/Year	Study Type	Number of patients Patient characteristics	Complicated Evolution	GER Strictures	Gastrostomy Feeds >3mtonhs	Severe tracheomalacia Respiratory Disease Recurrent Fistula	Predictors of Complicated Evolution	Conclusion
Castilloux et al 2010 (13)	Retrospective Review 1990-2005	134 patients A minimum of 3 and 15 months follow up data was required for inclusion for 1st year and long term models Median F/U 64mths (3-189) 66F Mean BW 2580g+/- 711g (1050-4334) Median gestational age 38wk (25-42) 8 (6%) were twins 45 (34%) had VACTERL EA Types Type A 9 (7%) Type B 3 (2%) Type C 112 (84%) Type D 2 (1%) Type E 8 (6%) 112 (84%) had Primary anastomosis 24 (18%) had gastrostomy at time of initial surgery 49 (37%) required gavage feeding Median length of hospital stay 22days (8-684)	Complicated evolution was defined as the occurrence of at least 1 of these complications: Severe GER Stricture Recurrent TEF Gastrostomy feeds>3mths Severe tracheomalacia Chronic respiratory disease 65 (49%)had complicated evolution <1yr 1 complication 33 2 Complications 14 >3 Complications 18 62/116 (53%)had complicated evolution >1yr 1 Complication 29 2 Complications 14 >3 Complications 19 Of the 65 patients with a complicated evolution <1yr, 41 (63%) had a complicated evolution >1yr Of the 69 patients without a complicated evolution <1yr, 21 (30%) had a complicated evolution >1yr	**Severe GER** moderate/severe esophagitis and or Intestinal Metaplasia and or need for fundoplication and or jejunal feeding **GER** <1yr 34% >1yr 43% **Strictures Requiring >1 dilatation** <1yr 16% >1yr 14%	<1yr 26% >1yr 19%	Severe Tracheomalacia Presence of cyanotic spells and bronchoscopy findings, the requirement of an aortopexy or tracheostomy or both <1yr 16% >1yr 14% Respiratory Disease Diagnosed by respirologist, oxygen dependence or both <1yr 9% >1yr 11% Recurrent Fistula requiring surgery <1yr 11% >1yr 12%	In the first year of life predictors of a complicated evolution were related to: **Patient** Twin birth Birth Weight <2500g VACTERL **The Malformation** Type A Long Gap Anastomotic Leak **Initial Respiratory Condition** Preoperative intubation Tracheal intubation>5days Inability to be fed orally by end of 1month >1year the predictors of a complicated evolution were: **The Malformation** Type A Long Gap Anastomotic Leak Inability to be fed orally by end of 1month Length of hospital stay >30d was associated with many of the predictor variables: Twin birth BW<2500g Preoperative respiratory problems Post-operative feeding difficulty The odds of a complicated evolution in children with initial hospital stay >30d was 9.3 and 3.5 times greater than in children discharged home before 30d at 1year and after 1 year respectively	Study was the first to show predictive factors of morbidity in EA-TEF In EA patients clinically significant morbidity occurs in >50% before and after 1year. Early predictors of short and long term morbidity were identified in this study These factors can be used to identify patients who will need more intensive follow up Significant problems can develop >1yr in some children who did not have problems <1yr Study limitations were small numbers in certain subgroups which limited analysis to models with single predictor variables. Hence some of the predictive variables reported may not be significant in adequately powered multivariate analysis. This limitation was overcome by using length of hospital stay which was related to multiple variables

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Anastomotic Complications	GER	Tracheomalacia	Feeding and Nutrition	Conclusion
Spitz et al 1987 (14)	Retrospective Review Between 1980-1984	148 EA patients EA Types Type A 10 Type B 3 Type C 128 (87%) Type D 1 Type E 5 Long Gap 13 Associated anomalies 69 (47%) GI Anomalies (excluding ano rectal) 18 (12.2%) Birth Weight <1000g 1 1001-1500 14 1501-2000 26 2001-2500 21 >2500 86 Operative Procedures Primary Repair 113 Esophagostomy/gastrostomy 23 Gastrostomy alone 2 22 had esophageal replacement (6-12mths) Gastric 17 Colonic 5 22 Deaths None in Type C, EA	Anastomotic leaks 24 (21%) Anastomotic strictures 20 (17.7%) About half of those with strictures had leaks No correlation between significant GER and leaks or strictures Recurrent TEF found on contrast study or on gastroscopy and/or bronchoscopy in 14 (12%) Statistically significant increase in rate of leak, stricture and recurrent TEF when braided silk was used as suture material	Presence and extent of GER was defined on radiological, endoscopic and pH metry Significant GER sufficient to cause life threatening episodes of aspiration 21 (18%) All 21 had Nissen fundoplication 15/21 had prior gastrostomy There was a significantly higher incidence of severe GER in cases undergoing gastrostomy 15/63, 23.8% vs patients having trans anastomotic feeding tube 6/50, 12% Less severe GER was managed conservatively	Degree of tracheomalacia assessed radiologically and at bronchoscopy Tracheomalacia severe enough to cause respiratory embarrassment 19 (16%) All 19 had aortopexy 7/19 had both GER and tracheomalacia and also had fundoplication 3/19 had tracheomalacia +GER+recurrent TEF Here the fistula was repaired first	Heights and weights were assessed at 6 months and 5 years Below 3rd centile 40 12/40 (21%) were Type C EA	In absence of abdominal distension EA repair can be delayed pending improvement of aspiration pneumonia LBW is not a contraindication for primary EA repair In infants with respiratory distress preliminary gastrostomy may be lethal. Emergency ligation of distal TEF is recommended Life threatening cardiac anomalies should be treated aggressively Advantages of preliminary endoscopy include assessment of length of proximal pouch, identification of upper pouch fistula or presence of laryngotracheal cleft Elective ventilation for 5 days post repair is recommendation reduce tension on anastomosis by swallowing and stabilizing neck in flexed position Silk sutures are associated with anastomotic complications No advantages for routine gastrostomy as it does not protect against anastomotic leaks., and may lead to severe GER Management of anastomotic leaks depends on time of occurrence Significant GER demands aggressive treatment with fundoplication as it can cause recurrent anastomotic strictures and may result in life threatening apneic episodes or aspiration pneumonia

							Severe tracheomalacia needs aortopexy Suspected recurrent TEF should be investigated by instilling contrast into esophagus via NG tube which is progressively withdrawn from the stomach into the esophagus with the patient in the prone position. Endoscopy and bronchoscopy should also be done. Symptoms include choking with feeding, recurrent pneumonia. Mortality in EA is related to severity of associated congenital anomaly

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of patients
Patient Characteristics</th><th>Contrast Study</th><th>pH Metry</th><th>Indications for Fundoplication</th><th>Fundoplication</th><th>Fundoplication Failures</th><th>Conclusion</th></tr>
<tr>
<td>Bergmeijer et al 2000 (15)</td>
<td>Retrospective review of prospective protocol for screening for GER

1984-1996</td>
<td>26 EA patients who had fundoplication

125 EA patients were repaired during study period

Pathological GER was diagnosed in 29 patients who had fundoplication
2/29 died from unrelated causes post surgery and 1 was ventilator dependant for 1yr and did not have follow up or surgery as per protocol so was excluded

20M, 6F

Mean BW 2280g (1590-32000
Gestation 31wk-full term

EA Types
Type A 4
Type C 22

Long Gap 10
Had Livaditis myotomy for repair

Mean follow up post fundoplication 5years (2-13), median 4yrs

Follow up examinations were not done by protocol.
Follow up examinations included esophagogastrography after 6 weeks and 1 yr and when instigated by complaints

8/26 had tracheomalacia based on symptoms
Based on bronchoscopy 5 had aortopexy
Tracheomalacia spontaneously improved in 3/8</td>
<td>Done at 10days and 6 weeks showed severe stricture in 19/26
9 of 19 had Livaditis myotomy-needing mean of 7 93-20) dilatations</td>
<td>Done for 24 hours without medication and a subsequent 24 hours on medication

Was offered to all patients with reflux in contrast study between 6-12 weeks
1 refused
7 could not be done due to stricture

Done in 18/26

Pathological reflux (reflux index >4%) in 17/18.
Mean acid reflux index was 14% (7.5-52)

Mean Number of reflux episodes 30 (21-250)

Mean number of prolonged reflux episodes (>5minutes) 10 (5-60)

Normal values in 1 with “Cyanotic spells)</td>
<td>Resistant stricture and pathological reflux in 20
Pathological reflux only 2
Recurrent aspiration/chest infection 2
Asthma 2</td>
<td>Done between 1-24 months post EA repair, mean 6mths, median 4 mths

Distal esophageal obstruction secondary to fundoplication was seen in none</td>
<td>Recurrent reflux in 4/26 (15%)

Failure rate compared to other studies

<table>
<tr><th>Study</th><th>Patients</th><th>Number of fundoplications</th><th>Number of recurrences</th></tr>
<tr><td>Curci 1988</td><td>31</td><td>14</td><td>5</td></tr>
<tr><td>Lindahl 1989</td><td>48</td><td>13</td><td>5</td></tr>
<tr><td>Wheatley 1993</td><td>80</td><td>21</td><td>7</td></tr>
<tr><td>Meyers 1990</td><td>498</td><td>33</td><td>2</td></tr>
<tr><td>Ashcraft 1998</td><td>222</td><td>77</td><td>9</td></tr>
<tr><td>Kubiak 1999</td><td></td><td>15</td><td>9</td></tr>
<tr><td>Current Study</td><td>125</td><td>26</td><td>4</td></tr>
</table>
</td>
<td>Medication use for reflux was not consistent during study period. In 1989 Domperidone was replaced by cisapride. Only some patients were given H2 blockers and none were given PPIs.

GER was investigated by contrast study and pH metry in all but endoscopy not routinely done. Results of endoscopy not given.

Failure of fundoplication was determined by symptoms and contrast study no endoscopy or pH metry mentioned

Protocolised follow up and treatment of GER recommended.

Fundoplication recommended for GER complicated by recurrent chest infections, severe strictures, cyanotic spells and vomiting and failure to thrive</td>
</tr>
</table>

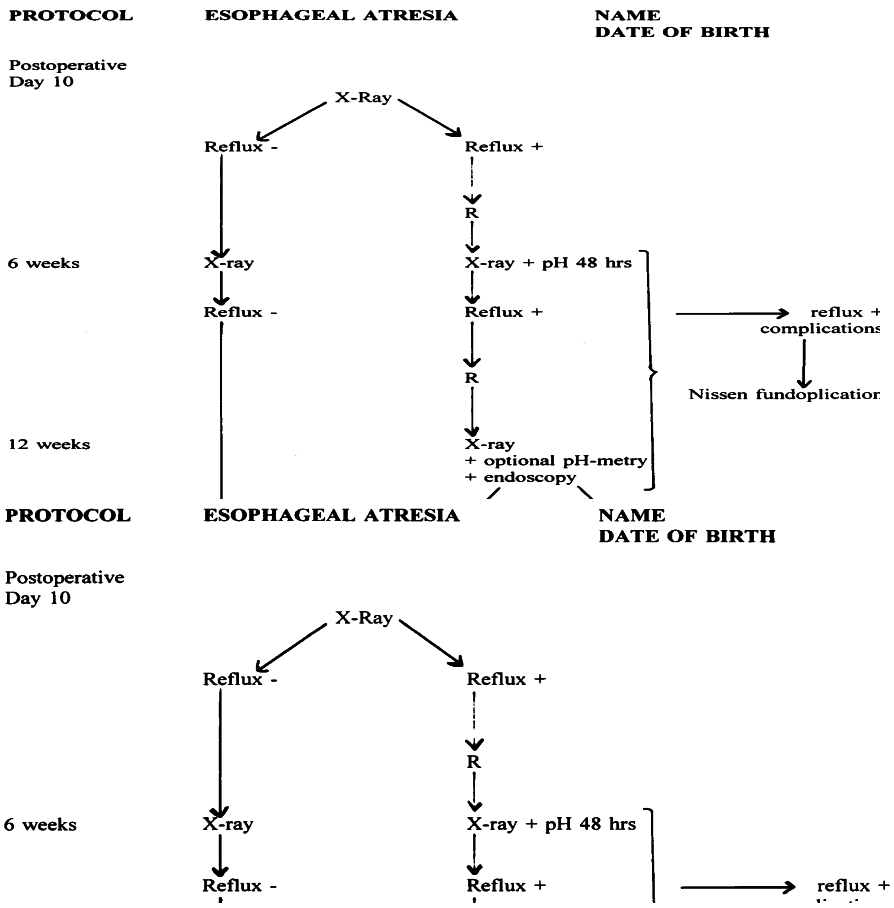

Figure 1. The postoperative treatment protocol.

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Methodology	Barium Study	pH Metry	Strictures	Fundoplication	Conclusion
Bergmeijer et al 1998 (16)	Prospective Study Between 1994-1995	26 16M, 10F 24 Type C, EA 2 Type A, EA Mean gestational age 37weeks (29-42) Mean BW 2160g(1000-3000) Associated anomalies 12 Duodenal atresia 1 1 patient died 2 had colonic interposition, they were excluded	Consecutive patients enrolled in study to establish : Efficacy of medical treatment of GER and stricture formation Relationship between anastomotic tension and GER Justification for doing fundoplication Protocol followed is shown above When GER seen in 1st Barium study, treated with Gaviscon after every feed and Cisapride GER evaluated after 6-12wks by Barium Swallow and 48hr pH Metry (24 hours with and 24 hours without treatment) Prospective evaluation repeated at 18wks, 6months and 1 year. All patients had follow up of at least 1 year	Reflux seen in 22/23 in 1st post op barium swallow and Gaviscon and cisapride started	19/22 had pH metry 5 had single pH Metry 14 had 2 consecutive pH studies (with and without medication) Without medication mean acid reflux index was 3.8% (0-11) for mild reflux in 12pts With medication the mean reflux index was 1.47% (0-3.2) In patients with mild reflux the number of prolonged reflux episodes lasting >5minutes decreased from a mean of 3.25 (1-8) without medication to 0.9 (0-5) on medication In 2 patients with reflux index >20% medication had no effect Reflux seen in 3/7 pts who had anastomotic tension and 8/15 without anastomotic tension	11/23 had stricture requiring at least 1 dilatation Mean 4 (1-9) 6/15 patients without reflux needed a mean of 3 dilatations (1-7) and 5/8 with reflux needed a mean of 5 dilatations (1-9) If a stricture was defined as one needing 3 or more dilatations: 4/15 non refluxing pts needed a mean of 4.2 dilatations (3-7) compared to 3/8 refluxing pts (5-9)	9/23 had Nissen fundoplication Early fundoplication (2-4months) done in 6 Indications: Respiratory 4 Resistant stricture 1 Respiratory with normal pH study 1 (this patient subsequently needed an aortopexy and authors concluded the fundoplication was unjustified) Late Fundoplication (22-24mths) 2 GER despite medication 1 Resistant stricture 1 All had successful outcome post fundoplication in the short term	GER based on Barium Swallow is the rule rather than exception in EA. Barium studies do not distinguish normal physiological regurgitation from pathological reflux. Hence pH metry is essential to discriminate between physiological and pathological reflux In this study infants with mean reflux index of 3.8% were categorized as having mild reflux where as in other studies <10% is considered normal Medication decreased reflux index and number of prolonged reflux episodes Only Gaviscon and cisapride were used in this study not H2receptor antagonists or PPIs Authors found a decreased stricture rate in this study compared to their study from 1984-85, 75% to 43% (11/23) They also found a decrease in the number of dilatations from 6.5 to 4.7. They concluded that anti reflux medication helps to reduce stricture formation and facilitate treatment of strictures The assumption that anastomotic tension leads to GER was not verified

								A Prospective protocol had help make a decision regarding need for fundoplication. Anti reflux surgery should be done based on clinical symptoms and objective measurements. No endoscopy done pre fundoplication in this study

GER in EA-TEF

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of Patients
Patient Characteristics</th><th>Post-Operative Complications</th><th>Long term complications</th><th>Quality of Life</th><th>Conclusion</th></tr>
<tr>
<td>Burgos et al
2010 (17)</td>
<td>Retrospective Review

Of colonic interposition between 1965-2008</td>
<td>96
Those >18yr contacted
9 (9.3%) died
65 long term survivors
44M
Median age 38 (19-48)

Mean age at surgery 2.9yrs (0.32-15)

Indications:
Not all were EA-TEF

1965-1990
Type A OA 16
Long Gap/Failed EA repair 18

1991-2008
Type A OA 9
Long Gap/Failed EA repair 8

Retrosternal graft 49
Mediastinal 16

Pyloroplasty was routinely done
Gastrostomy used till oral feeding established

Median follow up 33.3yrs (11-41)</td>
<td>
<table>
<tr><th></th><th>1965-1990 n=72 n (%)</th><th>1991-2008 n-24 n (%)</th></tr>
<tr><td>Salivary fistula</td><td>18 (25)</td><td>5 (21)</td></tr>
<tr><td>Stricture</td><td>9 (12)</td><td>2 (8)</td></tr>
<tr><td>Pneumonia</td><td>7 (10)</td><td>3 (12)</td></tr>
<tr><td>Intestinal obstruction</td><td>4 (5)</td><td>2 (8)</td></tr>
<tr><td>Atelectasis</td><td>4 (5)</td><td>2 (8)</td></tr>
<tr><td>Pneumothorax</td><td>3 (4)</td><td>1 (4)</td></tr>
<tr><td>Ulceration in esophagus</td><td>3 (4)</td><td>-</td></tr>
<tr><td>Mediastinitis</td><td>2 (3)</td><td>1 (4)</td></tr>
<tr><td>Abscess Wound disruption</td><td>2 (3)</td><td>2 (8)</td></tr>
<tr><td>Hiatal Hernia</td><td>1 (1)</td><td>-</td></tr>
<tr><td>Mortality</td><td>9 (11)</td><td>1 (4)</td></tr>
</table>
2 graft necrosis pre 1990, none since
</td>
<td>Mild reflux 23/53 (43%)
3 peptic ulceration in native esophagus left behind
Food impaction 8
Below 3rd centile for height and weight at end of growth period 5
Scoliosis 12/53 (22%)
Further surgery 15/53 (27%)
Esophageal adenocarcinoma 1</td>
<td>32(60%) with Karnofsky index of 80% or higher felt healthy
19(36%) had mild life style limitations (40-80)
2 had indexes<40% due to dysphagia or respiratory disease
Most eat normal meals

No correlation between QOL and incidence of complications</td>
<td>Outcomes given for whole group not EA specifically

Most patients with a colonic conduit had a patent conduit long term and satisfactory near normal QOL and life style

Gastro colonic reflux was not a major problem probably because of pyloroplasty

Ulceration of native esophagus left behind occurs as can carcinoma

Dysphagia and food impaction was probably related to original condition of EA</td>
</tr>
</table>

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	GER	Endoscopy	Strictures	Fundoplication	Conclusion
Lindahl et al 1995 (18)	Retrospective Review 1982-1992	7 9 Type A, EA Long Gap Mean BW 2620g (1530-3220) Waterston Group a 5 Group C 4 Delayed anastomosis and Livaditis myotomy in all Age at anastomosis mean 2.2months (1-3.5) No bouginage during waiting period 2 died from associated malformation Follow up 1.2-11.3year (mean 5.3)	All had severe GER with anastomotic strictures post delayed anastomosis	At Follow up All had endoscopy post fundoplication No stricture 3 had macroscopically normal mucosa 4 had macroscopic esophagitis 2 disrupted fundoplication 3 Intact fundoplication but was intra thoracic 2 competent wrap which was intra-abdominal 5 normal histology 1 moderate esophagitis 1 mild esophagitis	All had strictures requiring multiple dilatations 2 strictures failed to respond to dilatation even after fundoplication and were resected	All had fundoplication mean age 6months (3.1-10.8) Symptoms at follow up: 5 had excellent subjective results 2 had good results with occasional dysphagia 4 are on anti reflux medication due to esophagitis even after fundoplication 2 sucralfate 2 cisapride + sucralfate	Native esophagus is worth saving , But all patients had early complications of anastomotic stricture and all needed fundoplication to treat severe GER However PPI or H2RA not used to treat GER in this study, hence high rate to fundoplication could be due to this Recommend frequent endoscopic follow up and biopsy in EA even after fundoplication

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Indications for Fundoplication	Early Complications	Late Complications	Conclusion
Lindahl et al 1989 (19)	Retrospective Review 1981-1985	13/48 (27%) had fundoplication 1 died from associated anomaly 2wks post fundoplication and was excluded 12 had long tern follow up >2yrs Mean BW 2300g (14440-3040) 9 Type C, EA 3 Type A, EA 8 Lon gap 8 Livaditis myotomy 5 had associated anomalies 2 also had pyloroplasty with fundoplication Median age at fundoplication 1.3yrs (4.5mths-10.6yrs) All had endoscopy between 3-8mths post fundoplication Mean follow up 4.1yrs (2-6.4) Mean age at last follow up 6.3yrs (2.5-13.5) Last follow up 6 had endoscopy 5 had questionnaire 1 had esophagogastric fluoroscopy	6 anastomotic stricture not responding to dilatation due to GER 5/6 had distal esophagitis 3 recurrent pneumonia All had pathologic pH metry result All had reflux to upper third of esophagus on cinefluorography 1/3 had severe distal esophagitis 2 had severe vomiting and feeding difficulties Both had distal esophagitis 1 had severe esophagitis on routine endoscopy but was asymptomatic	No mortality or complication related to operation All 6 strictures responded to dilatation post fundoplication All 3 patients with pneumonias had no further chest infections requiring hospitalization 1 yr post fundoplication Vomiting ceased and feeding improved in 2 Distal esophagitis seen in 9 healed in all Endoscopy at 3-8mths showed intact fundal wrap in all	1 with Downs died. She had dad a redo 5 reflux recurrence and wrap disruption Recurrence of respiratory symptoms 4 Vomiting/feeding difficulty 1 Breakdown of fundal wrap occurred 1.5-2.5yrs post op Redo fundoplication 4 1 waiting for redo All 4 with a failed fundal wrap have Barrett's with gastric metaplasia 1 has dilated esophagus with competent wrap 6 are well with no symptoms	Around 25% of EA patients need fundoplication Recurrent respiratory symptoms are the main clinical manifestation of failed fundal wrap irrespective of primary pre op manifestation of GER Esophagitis post fundoplication is usually asymptomatic All patients with failed fundoplication had Barrett's with gastric metaplasia, hence regular endoscopies are needed for several years post fundoplication and in those with Barrett's for life long

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Electrogastrography (EGG)	pH Metry	Conclusion
Bokay et al 2005 (20)	Prospective Case Control Study	15 EA Patients 10 Controls EA Mean age 84 days (34-106) 8F, 7M Gestational age 34.6+/- 4.2 Controls Mean age 30days (17-39) 5M, 5F Gestational age 39.2+/- 2.8	EGG was done >3hrs (2hr pre-prandial and 1hr post prandial) after human milk or formula. Gastrostomy not used. Dominant electrical frequency, percentage of dominant electrical frequency in normal frequency range (2-4CPM), bradygastria (<2CPM), Tachygastria (4-10CPM), Dominant frequency instability coefficient and Dominant power was calculated Controls Distribution of gastric myoelectrical activity was normal with >60% dominance of 204CPM waves EA Dysrythmic myoelectrical activity seen Abnormal EGG patterns seen in 11/15 (73.3%) compared to 10% of controls during fasting The ratio of physiological 2-4CPM waves <60% in EA. These changes were significant The dysrythmia was mainly tachygastria during fasting Post prandially Significant increase in bradygastria and decrease in tachygastria in EA, compared to fasting state In controls increasing ratio of 2-4CPM waves No difference between breast fed and formula fed infants in EGG in controls No significant difference in dominant power before or after a meal between EA and controls	EA patients had frequent vomiting/regurgitation in 12/15 All patients with abnormal GER had DeMeester score >95th Centile 9/15(60%) were GER+ve from pH Metry There was not any difference in the distribution of myoelectrical waves (Bradygastria, 2-4CPM, Tachygastria), Dominant Frequency Instability Coefficient and Period Dominant Power of the stomach between GER+ and GER-ve groups either before or after a meal	Dysrhythmic gastric myoelectrical activity in 73% EA, with a significant difference in 2-4CPM group of waves Moderate dominance of tachygastria over bradygastria in EA. Dysrhythmia and tachygastria are associated with delayed gastric emptying and intrinsic neuropathic disorders of the gut. But gastric emptying not quantified in this study No significant difference in gastric myoelectrical activity between GER+ and GER-ve EA patients? due to small numbers or because disordered gastric myoelectrical activity is only one of the causes of GER in EA Abnormal gastric myoelectrical activity could result in feeding disturbances in EA

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Airway Obstruction (AO)/ Acute life threatening episode (ALTE)	Autonomic Disturbances	Tracheomalacia	Conclusion
Cozzi et al 2006 (21)	Retrospective Study between 1999-2002	25 EA pts who underwent ligation of distal fistula and/or feeding gastrostomy 10 died 15 survivors 11 (73%) maternal hydramnios 8 were born <37weeks 5 were Type C, EA 10 were Type A, EA 9/15 had feeding gastrostomy without esophagostomy Subsequently 5/9 underwent esophagostomy Eventually 11 had feeding gastrostomy and esophagostomy Premise behind study: Long Gap EA patients were studied before continuity of alimentary tract was established Gastrostomy feeds in a patient with blind lower esophageal stump excluded aspiration of gastric contents and stimulation of pharyngeal sensory endings and cervical esophagostomy excluded compression of intrathoracic trachea as cause of ALTE	AO was diagnosed clinically and classified as: Mild: signs of inspiratory airway obstruction Moderate: signs of inspiratory and expiratory airway obstruction Severe: presence of cyanotic attacks ALTE was defined as a sudden respiratory arrest nearly always associated with cyanosis which needed resuscitation maneuvers 13/15 had AO/ALTE 7 were premature 6/9 with gastrostomy but no esophagostomy had AO 4/6 had AO+ALTE 4/9 had ALTE but no AO The trigger was often accumulation of saliva in upper pouch Subsequently 5/9 needed an esophagostomy for this 5/11 with gastrostomy and esophagostomy had AO but no ALTE 6/11 had ALTE without AO, for which URTI was frequent trigger	Hyperhidrosis seen in 8 7/8 were premature Hyperthermia seen in 3 4 patients had episodic fever, hyperhidrosis, pallor, crying, diarrhea, dehydration, strabismus and tonic convulsions 4 had episodic bradycardia not related to hypoxemia	Presence or absence of tracheomalacia in 10 patients determined by bronchoscopy and/or presence of seal like cough 4 without tracheomalacia also had AO/ALTE syndrome	First study to investigate AO/ALTE in EA before establishment of continuity of alimentary tract The occurrence of AO/ALTE in infants with gastrostomy but without esophagostomy indicates that oral feeding and proximal GER reaching larynx are not essential prerequisites for AO/ALTE syndrome. Although GER in blind lower pouch could be reflexively responsible for respiratory symptoms/bradycardia Absence of ALTE preceded by AO in infants with esophagostomy gives indirect evidence that TC plays an important role in AO/ALTE syndrome Presence of AO, ALTE without AO in infants with esophagostomy and the presence of AO/ALTE in infants without tracheomalacia indicate TC/Tracheomalacia is not essential for the syndrome to occur. Presence of AO in absence of TC/or tracheomalacis strongly supports the concept of immature control of respiration as an important pathogenic factor for AO/ALTE syndrome. Abnormal respiratory control is part of generalized dysautonomia (hyperhidrosis, bradycardia, hyperthermia). Prematurity might have a role in this. In summary Oral feeding, proximal GER and tracheal compression (TC) might trigger AO/ALTE, they are not essential for AO/ALTE syndrome to occur. EA patients also have underlying problem with control of airway patency.

						Glossopexy might be a reasonable alternative to aortopexy or fundoplication in some EA patients with AO/ALTE syndrome

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Methodology	Results	Conclusion
Catalano et al 2011 (22)	Case control study	22 EA patients Repair between (2004-2008) 1 surgeon No tension No long Gap All Type C, EA Extra pleural approach No post-operative complications No stricture in contrast study All had endoscopy 1 month before impedance study and none had esophagitis Median Age 15months (3-40) 20 controls who were normal children with suspected GER of similar age	Reflux medication ceased 10 days prior to impedance (IMP) Symptom Diary: Heartburn Dysphagia Agitation Cough Regurgitation Parameters recorded: Number of acid/nonacid RBM Height of reflux Symptom Index Reflux Index (pHRI) abnormal >10% in <1yr and >4.2% in >1yr Bolus exposure index (BEI) abnormal in >1.4% in adults Mean acid clearing time (MACT) Mean bolus clearing time (MBCT) Results/Parameters evaluated for <1yr and >1yr and with regard to symptoms EA group compared to non EA group	**See Tables Below** In <1yr non acid RBM were significantly higher than acid RBM In >1yr acid RBM were significantly higher than non acid RBM Symptoms In 8/22 no symptoms recorded In <1yr symptoms mainly associated with non acid RBM In >1yr symptoms mainly associated with acid RBM Regurgitation, dysphagia and agitation were most associated with RBM Regurgitation seen most in <1yr Dysphagia seen most in >1yr pHRI was pathological in 10pts all >1yr Median pH RI in <1yr 2.6% was significantly lower than 8.1% in >1ys (p=.003) In absence of normal values for BEI/MACT/MBCT EA pts compared to non EA pts All EA pts had pathological BEI (if adult cutoff of 1.4% used) No significant difference between <1yr (6.1%)and >1yr (7.9%) Significantly higher BEI in EA (7.2%) vs non EA (2.8%), p<.0005 Median MACT (281sec) and MBCT (39sec) in EA were significantly longer than non EA 110 and 15sec respectively, p<.0005 for both Median MACT and MBCT were significantly shorter in EA pts without symptoms, 129 vs 368.2sec, p<.0005 and 26.5 vs 46.5se, p=.002 respectively	Incidence of GER in <1yr EApts would have been underestimated by conventional pH Metry alone Pathologic BEI with normal pHRI can be caused by GER and esophageal dysmotility. Hence more prolonged values were seen in EA vs normal children with suspected GER In younger children esophageal motility could be studied by pH-MII monitoring through BEI/MACT/MBCT and correlation established between symptoms, reflux and dysmotility. Significantly prolonged MACT and MBCT in EA pts confirms pathologic bolus transit in these patients. Interestingly asymptomatic EA patients had MACT/MBCT similar to controls with suspected GER, suggesting that dysmotility contributes to symptoms and reflux in EA patients Mean SI in EA patients was >80% correlated to esophageal dysmotility that worsens reflux and symptoms Symptoms in EA patients correlate more with impaired clearance Even in asymptomatic and tension free anastomosis, EA patients are at risk for GER and its complications and a follow up program even in asymptomatic patients is needed to avoid complications pH-MII allows indirect evaluation of esophageal motility pH-MII can be used to establish prognosis of esophageal disease and evaluate patients before anti reflux surgery

TABLE 1. MII events grouped based on age

EA patients	Total MIIe	Acidic MIIe	Nonacidic MIIe	High-reflux MIIe
Total (n = 22)	3884	918 (23.6)	2966 (76.4)	2830 (72.9)
≤1 y (n = 8)	1240	134 (10.8)	1106 (89.2)	934 (75.3)
>1 y (n = 14)	2644	784 (29.6)	1860 (70.4)	1896 (71.7)

Data represented in parentheses are percentages.
EA = esophageal atresia; MII = multichannel intraluminal impedance.

TABLE 2. Symptom events correlation

		Total RAS		Acidic RAS		Nonacidic RAS	
Symptoms	Symptom events	n	%	n	%	n	%
Heartburn	12	9	75	8	66	1	9
≤1 y	0	0	/	/	/	/	/
>1 y	12	9	75	8	66	1	9
Dysphagia	28	26	92	20	71	6	21
≤1 y	1	0	/	/	/	/	/
>1 y	27	26	96	20	74	6	22
Agitation	74	68	91	26	35	42	56
≤1 y	48	46	96	17	35	29	61
>1 y	26	22	84	9	34	13	50
Cough	170	102	60	64	30	38	19
≤1 y	64	40	62	22	34	18	28
>1 y	106	62	58	42	39	20	19
Regurgitation	102	100	98	37	36	63	62
≤1 y	94	93	98	31	32	62	66
>1 y	8	7	87	6	75	1	12
Total	351	305	86	155	44	150	42
≤1 y	220	179	81	70	31	109	50
>1 y	131	126	96	85	64	41	32

RAS = reflux-associated symptoms.

TABLE 3. Comparison between EA and control patients

Patients	BEI	pHRI
EA (n = 22)	*7.2 (2.5–13.7)	6.1 (1.3–13.8)
≤1 y (n = 8)	6.1	°2.6
>1 y (n = 14)	7.9	°8.1
GERD non-EA (n = 20)	*2.8 (1.4–5.7)	6.3 (0.4–13.4)
≤1 y (n = 10)	2.9	4.5
>1 y (n = 10)	2.7	9.5

Data represented in parentheses are in percentages. BEI = bolus exposure index; EA = esophageal atresia; GERD = gastroesophageal reflux disease; MII = multichannel intraluminal impedance; pHRI = pH reflux index.
* $P = <0.0005$ (for BEI). ° $P = 0.003$ (for pHRI).

TABLE 4. Correlation between pH and MII monitoring in EA group patients

	pHRI positive	pHRI negative
EA total (n = 22)		
BEI positive	10 (45.5)	12 (54.5)
BEI negative	0	0
≤1 y (n = 8)		
BEI positive	0	8 (100)
BEI negative	0	0
>1 y (n = 14)		
BEI positive	10 (71.4)	4 (28.6)
BEI negative	0	0

Data represented in parentheses are in percentages. BEI = bolus exposure index; EA = esophageal atresia; MII = multichannel intraluminal impedance; pHRI = pH reflux index.

TABLE 5. Mean values of clearance time in EA and control patients

	MBCT, s	MACT, s
EA (n = 22)*	39	281
Symptoms negative†	26	129
Symptoms positive†	46	368
GERD non-EA (n = 16)*	15	110

EA = esophageal atresia; GERD = gastroesophageal reflux disease; MACT = mean acid-clearing time; MBCT = mean bolus-clearing time.

* $P < 0.0005$ (for MBCT) and <0.0005 (for MACT).

† $P = 0.002$ (for MBCT) and <0.0005 (for MACT).

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Stricture	GER Dysmotility	Respiratory complications Tracheomalacia	Growth and Nutrition	Conclusion
Banjar et al 2005 (23)	Retrospective Review 1993-2004	41 26M, 15F Mean age of referral to tertiary center 15+/-29months 5 (12%) operated in tertiary center 36 (88%) referred from regional center 14 (34%) were premature EA Types Type C 37 (0%) Type A 2 (5%) Type E 2 (5%) Mean age at follow up 5+/-3.8yrs Associated anomalies 28 (68%) GIT 8 (20%) Primary repair 21 (57%) Delayed primary repair 14 (34%) Staged repair 6 (15%0	Defined as stricture if >dilatations required to improve swallowing Narrowing at anastomotic site 25 (61%) Dilatations required (1-12) 21 (51%)	GER by barium swallow or nuclear medicine 39 (95%) Hiatal Hernia 11 (27%) Fundoplication 24 (59%) Significant number of patients had persistent symptoms post fundoplication Correlations with GER see table below	Pulmonary complication >70% Persistent atelectasis 37 (90%) Chronic aspiration pneumonia in CXR 40 (98%) Asthma/hyper reactive airway 40 (98%) Chronic lung disease/O2 requirement 36 (88%) Tracheomalacia in bronchoscopy 12 (29%) 5 required aortopexy and 1 required tracheal stent Bronchiectasis by chest CT 7 (17%) 2 long gap 2 had gastric interposition 1 had colonic interposition Recurrent fistula 10 (24%) 4 had primary anastomosis Recurrent Fistula 10 (24%) Pulmonary function test in 16 (40%) Abnormal 88% Obstructive 3 Restrictive 8 Combined obstructive and restrictive 3 Normal 2	Failure to thrive 32 (78%) Gastrostomy feeds 26 (63%) Jejunostomy Feeds 9 (22%)	High percentage of GER (95%)and fundoplication (59%) GER was significantly related to dysmotility, atelectasis and aspiration pneumonia but not to type of surgery or development of chronic lung disease. GER is most common cause of respiratory problems in EA but other factors should not be overlooked Half of patients with bronchiectasis had esophageal replacement. Hence native esophagus should be used where possible and if replacement surgery is needed long term follow up and antibiotic prophylaxis is needed Due to similarity between symptoms of tracheomalacia and GER, vital to have bronchoscopy to differentiate between them However in this study GER was diagnosed only by contrast study/nuclear medicine and no pH metry/endoscopy done to confirm diagnosis of pathological reflux

Table 2 - Correlation of gastroesophageal reflux (N=41).

Variable	Gastroesophageal reflux n (%)	*P* value
Atelectasis	36 (92)	0.04
Dysmotility	3 (60)	0.04
Aspiration pneumonia	39 (100)	0.0001
Esophageal stricture	16 (46)	0.023
Esophageal narrowing (radiology)	25 (64)	0.07
Asthma/hyper-reactive airway disease	38 (97)	0.8
Surgery type		0.36
Primary	19 (49)	
Delayed repair	14 (36)	
Staged repair	6 (15)	
Chronic lung disease/O_2	35 (90)	0.09
Bronchiectasis	7 (18)	0.5
Pneumothorax	9 (23)	0.38

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Prognostic Scores	Results	Conclusion
Alsheri et al 2012 (24)	Retrospective Review Over 5 years	50 patients 5 deaths (10%) Male 27 (54%) EA Types Type A 2 (4%) Type B 1 (2%)Type C 39 (78%) Type D 4 (8%) Type E 4 (8%) Mean BW 2827g +/-794 Gestational age 38+/-3wks Associated congenital anomalies 36 (72%) GI 6 (12%) Median age at repair day 2 All on anti reflux medications 89.5% had early feeds via trans anastomotic feeding tube Median hospital stay 26days (1-383)	**Disease Specific**: Waterston McGill Spitz **Generic:** Score for Neonatal Acute Physiology II (SNAP II) Score for Neonatal Acute Physiology-Perinatal Extension (SNAP-PE) Prognostic scores calculated for each patient to assess ability of prognostic scores to predict early non mortality outcomes To compare performance of traditional disease specific scores to generic scores Mean SNAP Score 9.6+/=10.7 Mean SNAP-PE Score 13+/-14.4 No significant correlation between composite outcome and prognostic scores None of the scores were able to significantly predict non mortality outcomes although the generic scores outperformed the disease specific scores	**Outcomes**: Post-operative leak 8 Stricture requiring dilatation 18 5 had previous leak 13 had de novo stricture Median number of dilatations 5 (0-18) All were on oral feeds at 1year Recurrent Fistula 2 51% had poor composite outcome Early Complication <1month post repair Single early complication defining poor outcome	51% developed early complication None of the prognostic scores could predict non mortality outcomes Weakness of being a retrospective review Small sample size could obscure true correlations

GER in EA-TEF

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of Patients
Patient Characteristics</th><th>pH Metry</th><th>Conclusion</th></tr>
<tr>
<td>Bergmeijer et al
1999 (25)</td>
<td>Case Series
1994-1996</td>
<td>13 EA Patients
7F, 6M
Mean Gestational age 36wk (31-40)
Premature 7
Minor anastomotic tension 2
Minor anastomotic leakage 2
Contrast Study Normal in all (reflux on provocation was not considered abnormal)

During study period 48 EA repaired
Type A 3 (colonic interposition)
Type C 43
Type E 2

Exclusions:
All patients had pH metry between 8-16 weeks post surgery

Patients with GER complications or tracheomalacia were excluded

GER Complications 24
Failure to thrive
Anastomotic stricture
Respiratory infections
All were on anti reflux medications
8/24 (33%) had fundoplication

19/43 Type C EA patients had uncomplicated short and long term post-operative course for 1 year

4 who had delayed pH metry >16wks were also excluded

pH metry refused in 2</td>
<td>13 Type C asymptomatic EA patients with uncomplicated short and long term post-operative course for 1 year with no GER complications

Performed at mean 12.7wk (8-16)

Not on anti reflux medications

Mean Reflux Index 4.08% (1-9.8)

Mean total number of reflux periods with pH <4 was 21 (3-60)

Mean number of prolonged reflux episodes >5min 2.5 (0-9)

Results compared to values of pH metry from normal children (2.5-4.5mths)in Vandenplas study

<table>
<tr><th></th><th>EA</th><th>Normal</th><th>P value</th></tr>
<tr><td>Mean Reflux Index</td><td>4.08%</td><td>4.18%</td><td>NS</td></tr>
<tr><td>Mean total number of reflux episodes</td><td>21</td><td>20</td><td>NS</td></tr>
<tr><td>Mean number of prolonged reflux episodes</td><td>2.5</td><td>3.2</td><td>NS</td></tr>
</table>

No negative correlation between prematurity and extent or severity of reflux</td>
<td>First study to look at pH metry in EA patients without complications or GER and compare results from normal infants

24 hour pH metry values are the same in asymptomatic EA patients and asymptomatic children with normal anatomy

The values from asymptomatic EA patients can be used for evaluation of symptomatic EA patients with a clinical suspicion of pathologic GER</td>
</tr>
</table>

GER in EA-TEF

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of Patients
Patient Characteristics</th><th>Foker Procedure</th><th>Follow Up Results</th><th>Conclusion</th></tr>
<tr>
<td>Foker et al
2009 (26)</td>
<td>Case Series
Between 1995-2007</td>
<td>42 EA patients who had repair done using growth induction technique of Foker

60 had Foker for LG-EA
42/60 were at least 3 yrs post repair for short and long term follow up evaluation

31M, 11F

EA Types
Type A 28
Type B 10
Type C 4

18 had previous operations
TEF closure 5
Cervical spit fistula 13
Prior attempt at repair 7

3 deaths due to unrelated causes</td>
<td>Gaps average 5.7cms (3.3-12.5)
15 with gaps >6cms

14+/-12.9days in traction

GE junction kept below diaphragm

Age at first Foker operation 4days-2.5yrs

Some anastomotic tension seen in a few cases

Contrast study 2-3wks post repair to assess strictures and GER

All had dilatations

42/42 had fundoplication
12/42 (29%) had redo fundoplication with 16months</td>
<td>Average time of follow up 6.9 +/- 2.8yrs

3 Methods

First
Superficial questioning by telephone

Second
Mailed Questionnaire
Learning to eat
Problems after discharge
Hospitalizations
Dilatations
Stricture resections
Redo Fundoplications
Current Medications

Third
Endoscopy with biopsy
Esophageal ultrasound
Manometry

2/42 families could not be located but had been seen by pediatrician at 1 yr and were doing well

Questionnaire Results (N=28)

<table>
<tr><td>Feeding</td><td></td></tr>
<tr><td>Eat normally for age</td><td>27</td></tr>
<tr><td>Gastrostomy supplements</td><td>2</td></tr>
<tr><td>Aspiration symptoms</td><td>0</td></tr>
<tr><td>Continued Dilatations</td><td>0</td></tr>
<tr><td>GER</td><td></td></tr>
<tr><td>Fundoplication</td><td>28</td></tr>
<tr><td>No or mild GER symptoms</td><td>28</td></tr>
<tr><td>On anti reflux medications</td><td>16 (57%)</td></tr>
</table>

Both patients on supplemental G tube feeds were syndromal</td>
<td>Study shows suitability of the growth procedure for LG-EA, even those with rudimentary lower segments

Follow up evaluations indicate that there were no long term consequences in these children who had excellent functional result

No children still needing dilatations >3yrs post repair

In a sub group (28/40) questionnaire, endoscopy and biopsy indicate good to excellent outcomes. Uniform follow not done in all for results to be extrapolated to whole group

Patients treated by Foker technique seen comparable to short gap EA-TEF patients in their functional outcomes

Fundoplication was done based on presence of reflux in contrast study done post repair. Response to antacids is not mentioned before proceeding to fundoplication

Although contrast study, esophageal ultrasound and manometry are mentioned as being part of the follow up in some patients, results are not given

Absence of and presence of mild GER symptoms have been grouped together so hard to decipher how many were truly asymptomatic

Indications for continued use of anti reflux medication not given? Due to reflux recurrence post fundoplication. Only endoscopy done in 28, which showed esophagitis in 2 despite medication. No pH-IMP done to document how well the fundoplication was functioning

Authors have mentioned they attempted to take children of antacids, but not whether they had an exacerbation of GER when this was done</td>
</tr>
</table>

				Endoscopic Evaluation (N=15) **Endoscopic Appearance** | Gastric Metaplasia <4cm above LES | 13 Gastric Metaplasia >4cm above LES | 2 Visible esophagitis | 0 **Histology** | Upper Esophagus | Normal | 13 Esophagitis | 1 Eosinophils Present | 1 Lower Esophagus | Normal | 9 Mild Carditis | 2 Esophagitis | 2 Eosinophils Present | 2	Abnormal looking mucosa above GE junction is called “Gastric Metaplasia”, a better term could have been “Barrett’s” and subsequently classified as gastric or intestinal metaplasia. Not mentioned whether biopsies were taken from these areas of what appeared to be gastric mucosa above GE junction to see whether it was gastric or intestinal metaplasia Number of eosinophils presenting esophageal biopsies not mentioned to see whether it could be categorized as GER or EoE

GER in EA-TEF

<table>
<tr><th>Author/Year</th><th>Type of study</th><th>Number of Patients
Patient Characteristics</th><th>Anastomotic Leak</th><th>Strictures</th><th>GER</th><th>Tracheomalacia (TM)</th><th>Recurrent Fistula</th><th>Prognostic Score
Survival</th><th>Conclusion</th></tr>
<tr>
<td>Engum et al
1995 (27)</td>
<td>Retrospective Review
Between 1971-1993</td>
<td>227 EA patients
127M, 100F

7 were not repaired

Mean BW 2557g (1100-4460)
Mean Gestational Age 38wk (28-42)

EA Types
Type A 29 (13%)
Type B 2 (1%)
Type C 178 (78%)
Type D 5 (2%)
Type E 13 (6%)

Associated anomalies 146 (64%)
Duodenal Atresia 7
Malrotation 6

Gastrostomy

Routine Gastrostomy in first decade of study 76%
More recently gastrostomy only used in Type A, repair under tension or staged repair

68% complication rate with esophageal replacement procedures</td>
<td>Leaks 35 (16%)
Minor 33

Stricture developed in 17/35

Recurrent fistula in 1/35

94 % of leaks closed spontaneously</td>
<td>77/220 (35%)

Stricture defined as narrowing in contrast study which required 4 or more dilatations

Type A (n=27)
13/27 (48%) strictures
9/13 (69%) had GER
7/9 had fundoplication

Type B (n=1)
1 stricture
1 GER which was treated medically

Type C (n=174)
Stricture 57 (33%)
GER in 36/57 (63%)
18 treated medically
18 had fundoplication

Type D (n=5)
Stricture 5 (100%)
GER 2/5 (40%)
Both treated medically

Type E (n=13)
Stricture 1/13 (7/7%)
GER 1/1 (100%)
Treated medicaly</td>
<td>127/220 (58%)
71 (56%) treated medically
56 (44%) had fundoplication

<table>
<tr><th>Type</th><th>N</th><th>GER N (%)</th><th>Surgery N (%)</th></tr>
<tr><td>A</td><td>27</td><td>15 (56)</td><td>11 (73)</td></tr>
<tr><td>B</td><td>1</td><td>1 (100)</td><td>0</td></tr>
<tr><td>C</td><td>174</td><td>103 (59)</td><td>44 (43)</td></tr>
<tr><td>D</td><td>5</td><td>2 (40)</td><td>0</td></tr>
<tr><td>E</td><td>13</td><td>6 (46)</td><td>1 (17)</td></tr>
<tr><td>Total</td><td>220</td><td>127 (58)</td><td>56 (44)</td></tr>
</table>

Distal esophageal dysmotility seen on contrast study in 28%</td>
<td>32/220 (15%)

Incidence of TM in different EA Types

Type A 16.7%
Type C 14.6%
Type E 15.4%

Aortopexy 2
Tracheostomy 11</td>
<td>6/220 (3%)
4 Type C
1 Type E
Stricture in 3/6 (50%)
All were Type C</td>
<td>Overall 12% died
Type C 8
Type A 4

Waterston Criteria (N=197)
Group A 41 21.4%
100% survived

Group B 116 (60.4%)
96.6% survived

Group C35 (18.2%)
88.6& survived</td>
<td>Despite improvements in patient care and survival rates, anastomotic complications including leaks, stricture, recurrent TEF are commonly seen.

Strictures treated with dilatation and aggressive medical treatment of GER failing which fundoplication

Clinically significant TM nor apneic spells seen in Type A, in spite of high incidence of GER

Incidence of TM similar in different EA Types

Improved survival rates were noted irrespective of Waterston criteria, which may be outmoded</td>
</tr>
</table>

Author/Year	Study Type	Number of Patients Patient Characteristics	Indications for fundoplication (NF) Pre op Investigations	Reflux recurrence post Fundoplication Redo Fundoplication	Predictors for failure of Fundoplication	Conclusion
Lopez-Fernandez et al 2014 (28)	Retrospective Review Between 1992-2011	360 217M, 143F Median Gestational Age 37wk (23-42) Median BW 2680g (465-4600) Median birth height 47cm (24-59) Prematurity 27.1% **Comorbidities**: Neurological Impairment (NI) 100 (27.1%) **EA 50 (13.9%)** Congenital diaphragmatic hernia (CDH) 22 (6.1%) Abdominal wall defects 6 (1.7%) Stricture 35 (9.7%) Previous Abdominal Surgery 98 (27.2%) Median age at fundoplication 3.06yrs (.04-20.7) Median weight 12kg (2-77) Median Height 102cms (36.7-165.5) Open NF 169 (54.4%) Laparoscopic 164 (45.6%) Conversions 9 Concomitant gastrostomy 149 (41.4%) Pyloroplasty/pyloromyotomy 80 (22.2%) Median Follow Up 6.7yrs (.01-18.7) **Post Op Complications;** Wound infection 10 Dumping 9 Gastrostomy related 8 Intestinal obstruction 7 Evisceration 5 Chylothorax 2 Pneumothorax 1 29 (8.1%) died	Fundoplication done in symptomatic GER unresponsive to medical treatment, objectively demonstrated by pH Metry/impedance/dual pH Metry/contrast series showing hiatal hernia and/or GER/ and/or biopsy proven esophagitis on endoscopy Reflux symptoms: Vomiting 275 (76.4%) Heartburn/Chest pain 81 (22.5%) Respiratory 207 (60.3%) pH Metry (often bichannel) 210 (58.3%) Barium Meal 193 (53.6%) Endoscopy and biopsy 171 (47.5%)	**Recurrent GER 42 (11.7%)** Symptoms Vomiting 23 Respiratory 13 Dysphagia 7 Heartburn 5 Asymptomatic 7 (wrap ascent/insufficiency diagnosed on Barium) Investigations: Imaging 28 Endoscopy 18 pH Metry 13 Comorbidities NI 13 **EA 12** CDH 7 AWD 1 35/42 had Redo NF Median time between first and second NF 1.01yrs (.02-8.4) **9/35 (25.7%) had second GER recurrence** 5/35 had another redo 3 esophageal replacement 1 esophagogastric disconnection Comorbidities: EA 9 NI 2 CDH 1 1 had 3rd redo NF	Male p .029 **EA p=.007** CDH p=.008 Previous abdominal surgery p=.003 Young age at surgery p=.001 Low weight at surgery p=.002 **Logistic Regression:** Males p=.016, OR 2.93 **EA** **31.6% Failure Rate** **p=.043, OR 2.5** CDH p=.002 OR 6.57 Age at surgery was negatively associated with NF failure p=.005 **Predictors for Redo NF, with need for third NF** **EA p=.015**	For EA patients risk of NF failure is higher than general population Young age at surgery for an independent predictor for failure of NF and EA patients are often operated on for NF at young age Failure rate of redo NF is high 25.7% vs 9.7% for first NF, this was particularly noticeable in EA patients After redo NF failure apart from another redo, other options especially in EA patients are esophageal replacement or esophagogastric disconnection

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Complications	GER	Mortality	Conclusion
Montgomery et al 1993 (29)	Retrospective Review Between 1971-1987	110 EA Patients 66M, 44F Type E, EA were excluded Mean BW 2770g (1420-4120) 35% <2.5Kg 9 <1.8Kg Mean gestational age 38wk (32-42) Associated anomalies in 49 (45%) Primary anastomosis 93 Initial gastrostomy 12 3 with LG had colonic interposition Circular myotomy 14	100/110 had Barium study Anastomotic leak 19 Recurrent fistula 11 Routine dilatations not done but only in patients with symptoms of stricture or when stricture seen in barium study 60% needed dilatations 12/14 myotomy patients needed dilatations Foreign body in esophagus 33 pts (73 times)	Reflux seen in Barium 28 (30%) Reflux symptoms >50% Vomiting 40% Respiratory 67% Dysphagia 71% Medical treatment Posture Thickening feeds Antacids Metoclopromide Fundoplication 9 4/9 had myotomy	Overall mortality 12% (13/110) BW <1.8kg had a higher mortality 45% **Early mortality <6months: 6** Mainly caused by prematurity and associated anomalies **Late mortality >6months 7** Mainly due to respiratory complications **4/7 due to GER/aspiration** 2/7 due to prematurity 1 had myotomy, died due to stricture/perforation during dilatation **All 7 had symptoms of severe GER:** Aspiration 6 Vomiting 5 Esophagitis 1 None had fundoplication	EA plays a big role in morbidity and mortality of EA patients especially in first year of life More aggressive treatment of reflux might have prevented late mortality Myotomy patients had more complications and symptoms of reflux. 30% had fundoplication vs 8% of whole group. However myotomy group did not have higher mortality rate

Author/Year	Study Type	Study Methodology	Results	Conclusion
Montedonico et al 1999 (30)	Animal Study	Study Group 20 rats 15mm of cervical esophagus was resected and then re anastomosed Controls 8 rats Esophageal transection and re anastomosis **Hypothesis:** Gastroesophageal pressure barrier is weakened by anastomosis under tension Manometry 3 variables: **Lower esophageal sphincter pressure (LESP)** Difference between intragastric pressure and the peak of the more distal component of the pressure profile **Crural sling pressure (CSP)** Difference between baseline pressure and the peak of the more proximal component of the pressure profile **Length of the intra-abdominal segment of the esophagus (LIAE)** Distance between the onset of the first component and the respiratory inversion point when the esophagus becomes intra thoracic Control values measured and manometry repeated 1 week after surgery when feeds had been established	5 rates from the experimental group died due to anastomotic leaks In comparison with the baseline measurements LESP and LIAE were significantly decreased 1 week after esophageal resection but did not change after esophageal transection CSP did not change significantly	Anastomosis under tension weakens the anti-reflux barrier by decreasing the sphincteric pressure and the length of the intra-abdominal esophagus, thereby facilitating GER The use of an animal model with no intrinsic structural anomalies confirms the fact that the changes to the anti-reflux barrier are secondary due to traction caused by anastomosis under tension

GER in EA-TEF

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of Patients
Patient Characteristics
Survival</th><th>Anastomotic Complications
(Leak, Stricture, Recurrent TEF)</th><th>GER</th><th>Bronchoscopy</th><th>Conclusion</th></tr>
<tr>
<td>McKinnon et al
1990 (31)</td>
<td>Retrospective Review
Between 1976-1989</td>
<td>64 EA Patients

BW 950-4000g
Gestational age 30-40wks
Prematurity 26
Associated congenital anomaly 35
Livaditis technique 16
2 died

Waterston
Category A survival 12/12 (100%)
Category B survival 14/14 (100%)
Category C survival 30/36 (83%)
Overall survival 56/62 (90%)

Early mortality and overall mortality was higher in LG EA
Late mortality was same in both groups
<table>
<tr><td>Mortality</td><td>Minimal Gap 36</td><td>LG 26</td></tr>
<tr><td>Early</td><td>2 (5.5%)</td><td>4 (15.4%)</td></tr>
<tr><td>Late</td><td>5 (13.9%)</td><td>4 (15.4%)</td></tr>
<tr><td>Total</td><td>7 (19.4%)</td><td>8 (30.8%)</td></tr>
</table>
</td>
<td>Anastomotic leaks identified by saliva in chest drain and contrast studies

Strictures defined as major if dysphagia and >4 dilatations required

Minor if asymptomatic or <3 dilatations required

Dilatation initially bougie, then balloon in radiology and more recently during endoscopy

Overall complications 43 (69%)
Major 14
Minor 29
!0 had 2 complications

Anastomotic leak 21% of 62
2 Major
11 minor

Strictures 14 (23%)
Major 18
Minor 9

Recurrent TEF 3 (5%)

Long Gap 26
Minimal gap 36

Of 36 with minimal gap
32 Type C (mid tracheal fistula)
2 Type C with distal cervical fistula
2 Type E, EA

Of 26 with LG
20 Type C with distal carinal fistula
4 Type A
2 Type B

Majority of anastomotic complications occurred in LG

2 with LG had major leaks

Associated congenital anomalies in 15/26 LG (58%) and those with minimal gap 20/36 (55%)</td>
<td>GER was more frequent and severe in LG EA
7/22 LG EA had fundoplication

1/34 (3%) with minimal gap had fundoplication</td>
<td>Done in 56

Observations:

Level of fistula: carinal, mid tracheal or cervical

Anatomical variants

Presence and severity of tracheomalacia

Position of the aortic arch

Carinal fistulas were associated with LG EA

Mid tracheal or cervical fistulas were associated with minimal gap EA</td>
<td>Most important factor in the pathogenesis of anastomotic complications is tension on the anastomosis

The most important determinant of tension is the anatomy of the anomaly

Infants with LG were 5 times more likely to develop a leak, stricture or recurrent TEF

A long gap (LG) was predicted by a bronchoscopic finding of carinal TEF

Hence bronchoscopic findings are important in the prediction of post operative complications and outcome</td>
</tr>
</table>

Anastomotic complications

Complication	Minimal Gap 36	LG 26	Total 62
Major Leak	0	2	2 (3%)
Minor Leak	5	6	11 (18%)
Major Stricture	12	6	18 (29%)
Minor Stricture	2	7	9 (15%)
Recurrent TEF	1	2	3 (5%)
Total	3 (8%)	11 (42%)	14 (23%)

Analysis of major complications (14) according to pathogenic factors in 13 EA-TEF patients

Complication	N	Pathogenic Factor (N)
Leak	2	Tension (2)
Stricture	9	Tension (7)
		GER (4)
		Haight Anastomosis (2)
Recurrent TEF	3	Tension (2)
		Minor Leak (1)
		Technical Error (1)

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Stricture	GER	pH Metry	Video Manometry	Conclusion
Kawahara et al 2009 (32)	Retrospective review of consecutive patients between 2002-2007	**Group A** **Open Repair** 10 EA Mean BW 2450g (1464-2908) Mean Gestational age 38wk (33-41) Group B Thoracoscopic Repair 7 EA Mean BW 2814g (2460-3710) P=.02 Mean Gestational age 40wk (37-41), p=.15 Prenatal diagnosis similar in both groups, p=.33 Associated anomalies similar in both groups, p>.99 Placement of gastrostomy similar in both groups, p=.30 All were Type C, EA in both groups Age at primary repair similar 2d in Group A (0-12) and 1 day (1-3) in Group B, p=.37 Incidence of minor leak similar in both groups, p>.99 Follow up period similar Group A 51mths (24-75) Group B 51mths (43-70) P=.72	2 in Group B needed dilatation, p=.15	Fundoplication done for frequent pneumonia/hematemesis in 2 patients each in both groups, p=.60 1 pt in Group A who had fundoplication on clinical grounds (cardio respiratory distress requiring tracheostomy) Contrast study also showed GER. This patient subsequently died at 30mths from cardio-pulmonary failure 3/4 had neurological impairment All 3 had absent distal esophageal peristalsis on manometry Remaining 13 did not require aggressive medical treatment H2RA given for 3mths in 2 pts in Group A and 1 pt in Group B 1 pt in Group B needed H2RA for 7 months because contrast showed free reflux and needed 3 dilatations for recurrent anastomotic strictures although otherwise asymptomatic and had normal pH Metry	All had pH Metry except 1 case in Group Done at similar time in both groups Group A 41days (31-112) Group B 39days (24-119) P=.87 Median values for Reflux Index in Group A 5.5% (0.7-24.6) and 3.7% (0.3-56.8) in Group B, p=.71 Median esophageal acid reflux time in Group A 0.5min (0.1-1.4) and 0.5min (0.1-1.3) in Group B, p=.87	Swallows done using contrast material Done at similar times in both groups Group A 47Days (28-116), 39 days in Group B (24-127) P=.92 Lack of esophageal contractions in anastomotic region in all patients Esophageal motor patterns shown by tographic analysis were classified into 2 groups based on presence/absence of peristalsis in distal esophagus Aperistalsis in 1 patient in Group A and 3 in Group B, p=.26 Synchronous peristalsis in distal segment in 1 in Group A and 3 in Group B Sequential Peristalsis seen in 7 in Group A (78%) and 1 in Group B (14%), p=.04	No evidence that minimally invasive thoracoscopic repair of EA leads to a reduction in the disturbance of esophageal motor function In fact peristaltic pattern of esophageal contractions seen more frequently after open repair Thoracoscopic repair had no influence on development of subsequent GER and pH pattern and incidence of fundoplication similar in both groups This suggests disorders of esophageal motor function result from an inherent abnormal innervation of the esophagus rather than intra operative denervation Only patients needing dilatation of stricture were post thoracoscopic repair Selection of type of operative procedure was not standardized as it was a retrospective study

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	GER Fundoplication	pH Metry	Video Manometry	Conclusion
Kawahara et al 2007 (33)	Retrospective Review	29 EA patients Median age 4 years (1mth-19yrs) EA Types Type A 3 Type B 1 Type C 25 All had primary anastomosis	6/29 had fundoplication prior to study EA Types Type A 1 Type C 5 9/23 had fundoplication subsequent to study for vomiting and/or recurrent chest infections despite acid suppression EA Types Type A2 Type B 1 Type C 6 14/29 had no GER symptoms and were not on treatment	Done in 16pts Group 1 (7 patients) Median Reflux Index was 38.1% (11.7-56.8) Group 2 (9 patients) Median Reflux Index was 4% (0.7-10.2) There was a significant difference in the Reflux Index in patients with the two patterns, p<.001	Done with swallows of contrast material Lack of esophageal contractions in anastomotic region in all 100% Relaxation of LES occurred with swallows 100% Patients were classified into 2 groups : Group 1 (17 patients) Contractions were absent in distal esophagus with swallows Marked stasis of contrast material given orally. When contrast refluxed into esophagus from stomach it was not empties soon and showed to and fro movement in esophagus with respiration 6 /17 had prior fundoplication 9 /17 with symptomatic GER had subsequent fundoplication 2/17 had no GER symptoms Group 2 (12 patients) Contractions seen in distal esophagus with swallows Only temporary stasis or oral contrast seen in esophagus which gradually emptied with deglutition Contrast refluxed from stomach it was cleared with luminal closure proceeding down the esophagus None of 12 had symptomatic GER requiring treatment Presence or absence of distal esophageal contractions was significantly correlated to development of GER, p<.001 Concurrent manometry and pH Metry done in 7 to investigate esophageal motor response to acid reflux	Lack of distal esophageal contractions indicating an impaired clearing capacity was the key determinant for GER and need for fundoplication n EA patients Universal absence of esophageal contractions at anastomotic site could be due to injury to vagus during surgery Absence of distal esophageal contractions in some could be congenital because esophageal dissection during surgery rarely reaches cardia Useful to investigate esophageal contractions in early post-operative period to predict need for subsequent fundoplication Retrospective study so no correlation between esophageal dysmotility and esophageal histology at endoscopy possible. Also not possible to look at esophageal motility at early and late post-operative stages.

					In 3 with Type ! pattern drop in pH lasted despite repetitive swallows In 4 with Type 2 the esophageal pH gradually increased with swallow induced esophageal contractions	

GER in EA-TEF

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of Patients
Patient Characteristics</th><th>Stricture</th><th>GER
Fundoplication</th><th>Subjective Symptoms
Post fundoplication</th><th>Endoscopy/Histology</th><th>Conclusion</th></tr>
<tr>
<td>Lindahl et al
1993 (34)</td>
<td>Retrospective Review
1981-1995</td>
<td>55 EA patients
51 Type C
4 Type A, delayed repair

27 had associated anomalies
GI 3

Waterston
Group A 23
Group B 7
Group C 28

Early/Late Mortality 12
All were in Waterston Group C

43 had follow up

39/43 had endoscopy at mean 7.6yrs (2-11)

39 Patients
Type A 2
LG-EA 10
7/10 had Livaditis myotomy

4 had recurrent TEF</td>
<td>3 Strictures needed repeated dilatations

9 had foreign body occlusions requiring endoscopic removal</td>
<td>9 Fundoplication for GER symptoms

3/9 had 2 fundoplication

Strictures healed post fundoplication</td>
<td>Subjective Results
(Desjardin's classification)

Excellent 25
Good 10
Fair 4

8/10 with good results had mild respiratory symptoms
2/10 had mild dysphagia

All 4 with fair results had recurrent chest infections</td>
<td>39 patients
No biopsies from 2 with normal macroscopic appearance

Endoscopy
Normal in 17
Esophagitis 20
Barrett's 5
Hiatal Hernia 10
3/9 with fundoplication had wrap disruption
2/3 had 2 fundoplications

Histology
Normal 13/37
Esophagitis 2
Mild 17
Moderate 4
Gastric Metaplasia 3

2/5 with Barrett's actually had moderate esophagitis

1 endoscopic esophagitis had normal histology

5 endoscopic normal esophagus had histological esophagitis

Risk Stratification for mucosal changes

<table>
<tr><th>Group</th><th>No</th><th>Normal</th><th>Esophagitis</th><th>Esophagitis + Gastric Metaplasia</th></tr>
<tr><td>Gap Length</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Long Gap</td><td>10</td><td>2</td><td>5</td><td>3</td></tr>
<tr><td>Normal Gap</td><td>27</td><td>11</td><td>16</td><td>0</td></tr>
<tr><td>Subjective Result</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Excellent</td><td>23</td><td>8</td><td>14</td><td>1</td></tr>
<tr><td>Good</td><td>10</td><td>5</td><td>5</td><td>0</td></tr>
<tr><td>Fair</td><td>4</td><td>0</td><td>2</td><td>2</td></tr>
<tr><td>Total</td><td>37</td><td>13</td><td>21</td><td>3</td></tr>
</table>

Histological changes correlated poorly with symptoms

Gap length had a positive correlation with severe histological changes (gastric metaplasia)</td>
<td>Majority of EA patients had excellent or good subjective result post repair

However subjective symptoms correlated poorly with endoscopy and histology. More than half of patients with excellent results had esophagitis, 1 had gastric metaplasia

Long gap was a predictor for gastric metaplasia

Esophagitis can occur in the absence of any predictive factors

Endoscopy correlated well with histology. However there were 5 false negative endoscopies

2 macroscopic Barrett's had only esophagitis and in 3/5 it correlated with gastric metaplasia

Endoscopic and histological changes some of which are potentially pre malignant 9gastric metaplasia) are common in EA patients

Regardless of symptoms long term endoscopic follow up is warranted in all EA patients</td>
</tr>
</table>

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Digestive Symptoms	Respiratory Symptoms	Nutrition	Quality of life	Conclusion
Legrand et al 2012 (35)	Retrospective Review Between 1989-1998 In 2008 all patients invited to have their digestive, nutritional, respirator status and QOL assessed	81 EA patients with Type C, EA 6 died 14 lost to follow up 4 refused 57/81 (70%) were available for study Mean age 13.3 yrs (9.5-18.5) Mean gestational age 37.7wks (Mean BW 2607gms 15 (26.3%) premature 16 (28%) had IUGR 67% had associated anomalies Initial gastrostomy in 8 (14%) Secondary gastrostomy 2 No esophageal replacement	**Digestive Symptoms** **Dysphagia** Moderate Extra drinks at meal times or vomited after food impaction <1/month Severe Vomited after food impaction <1/day but >1/month Extreme Frequent food impaction and vomiting >1/day Meal duration (abnormal >30min) Early satiety Abdominal Pain **GERD** (heartburn/regurgitation) And/or pH metry Endoscopy in last year with RI >5% or erosive reflux disease respectively 85% had GERD prophylaxis till age 2 13% were still on GERD medications 39% had fundoplication 24 (46%) had at least 1 dilatation for stricture in past Dysphagia seen in 41 (65%) Independent of presence of anastomotic stricture in neonatal period Moderate dysphagia 26% Severe 21% Extreme 14% GERD seen in 22 (35%)	**Respiratory Symptoms** Chronic cough (>2months/year) Barking cough (Tracheomalacia) Bronchitis Dyspnea with exertion Cough 12 (19%) Dyspnea on exertion 21 (33%) Barking cough 24.5% Bronchitis 42% 37% had no respiratory symptoms Spirometry done in 36 Abnormal 75% Proximal obstruction and/or pulmonary distension 50% Restrictive 11% No other factor (prematurity, IUGR, associated anomalies, VACTERL, dilatations, gastrostomy, fundoplication, dysphagia, GERD)was significantly related to respiratory symptoms or spirometry results	Mean BMI 18.4kg/m2 Mean weight for age ration 102.7% Mean height/age ratio 99.2% Weight/height z score 0.24SD Abnormal nutritional status 17 (27%) 9 (16%)were overweight 5 (9%) were undernourished Past history of GERD was significantly associated with a lower weight/height z score , p=.02 No other factor (prematurity, IUGR, associated anomalies, VACTERL, dilatations, gastrostomy, fundoplication, dysphagia, actual GERD, chronic cough or dyspnea on exertion) was significantly related to nutritional status	Assessed by PedsQL 4.0 8-12yrs 13-18yrs Applied in parallel to patients and parents Compared with scores from databank of 5079 healthy children and 574 children with chronic disease (asthma/diabetes) Median QOL score of 80 chosen as cut off to allow comparison with factors associated with higher and lower scores Physical health score was lower in children with GERD (83/100 vs 88/100), p<.05 No other factor influenced physical health Emotional score was lower with dysphagia (69/100 vs 78.5/100), p=.02 Emotional score was lower with dyspnea at rest(65.5/100 vs 76.5/100), p=.03 No other factor influenced social score School score lower with malformation (72/100 vs 83/100), p=.02 Especially cardiac malformations (59/100 vs 80/100), p=<.03 Total QOL score lower in Type C EA than in healthy children, p<.05 Total QOL higher in Type C, EA than in other chronic disease, p<.05	One of the first studies to look at digestive, nutritional, respiratory complications and QOL in EA, Type C at long term follow up Even though there was 70% participation characteristics at birth of participating and non participating patients was similar Feeding difficulties were under reported unless asked for Digestive symptoms were more common than respiratory symptoms GERD was associated with under nutrition but no other digestive or respiratory symptom Nutritional status of cohort was similar to normal population without dysphagia or GERD Chronic cough regresses with age, 24% (9-15yrs), 9% (>15yrs) Possibility of bias as not all had spirometry Many EA Type C patients had long term functional respiratory, digestive and nutritional problems, and QOL in EA Type C was lower than healthy children. However it was better than in other chronic diseases Regular multidisciplinary follow up to adulthood is needed

			No association between dysphagia or GERD with other factor (prematurity, IUGR, associated anomalies, VACTERL, dilatations, gastrostomy, fundoplication, chronic cough or dyspnea on exertion) Prolonged meal times 15 (24%) Early satiety 15 (24%) Recurrent abdominal pain 15 (24%) 19% had no digestive symptoms			Factors associated with a lower QOL score on multivariate analysis were : Prematurity (OR 6.1) Barky cough (OR 9.4) GERD (OR 6.1) Other factors : IUGR, associated anomalies, dilatations, gastrostomy, fundoplication dysphagia, dyspnea on exertion, CHD, Boys, VACTERL, under nutrition, long meals, early satiety, recurrent abdominal pain were not significantly associated with a lower QOL	

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of Patients
Patient Characteristics</th><th>Clinical Outcomes</th><th>Scintigraphy</th><th>Conclusion</th></tr>
<tr>
<td>Lopes et al
2007 (36)</td>
<td>Retrospective Review
2000-2003</td>
<td>15 EA Patients
8M
Median age 31mths (12-42)

Group 1 (6)
Long Gap EA (2-6cm)
Type A 2
Type C 3
Type D 1
All primary anastomosis
Anastomotic tension 6
Complete mobilization of distal esophagus 3
Foker 1
Significantly more prematurity, gastrostomy and fundoplication than Group 2
Follow up median 26.5months

Group 2 (9)
Non Long Gap EA (<2cm)
All Type C
Follow up median 31months</td>
<td>Severity of symptoms graded based on presence or absence of and severity of digestive (eating habits, GERD, dysphagia, abdominal pain)and respiratory (chest infection, asthma, chronic cough) symptoms

These results were further scored: (Table 1)
Excellent: Scores 0 and 1
Good: Score 2
Poor: Score 3

Patients who had fundoplication had pH metry. Acid suppressive medication and prokinetics were ceased 2 weeks prior Reflux Index >5% was considered positive for GER

At follow up all were on full oral intake
All had normal nutritional status and growth velocity
No respiratory disease or reflux related symptoms for last 6 months

Symptom Scores
<table>
<tr><th>Scores</th><th>Long Gap 6</th><th>Non Long Gap 9</th></tr>
<tr><td>0 (%)</td><td>4 (66.7)</td><td>7 (77.8)</td></tr>
<tr><td>1 (%)</td><td>2 (33.3)</td><td></td></tr>
<tr><td>2 (%)</td><td></td><td>2 (22.2)</td></tr>
<tr><td>3 (%)</td><td></td><td></td></tr>
</table>
An excellent outcome score (0 and 1) was found in most children (100%) in Group 1 vs 77.7% in Group 2) and patients were generally asymptomatic (66.7% in Group 1 vs 77.8% in Group 2), p >.05

5 children who had fundoplication showed no GER on pH Metry</td>
<td>Done after overnight fast.
No prokinetics for 2 weeks

Data collected:

Esophageal Transit Time
Time from swallowing onset to residual activity of 10% of maximal activity
ETT was graded as per Somppi classification :

Normal
90% transit time up to 17s

Minor Dysfunction
90% transit time 18s-5min

Major Dysfunction
90% transit time >5min

Gastric emptying related to time taken for 50% (t1/2) material to leave stomach based on Estevado-Costa data:
Delayed Gastric Emptying
t1/2 > 85min

ETT and Gastric t1/2 used to quantify degree of esophago-gastric dysmotility (Table 2)

Results:
All 15 had quantitative and qualitative abnormality
Esophageal hypo contractility seen
Bolus accumulated in lower two thirds of esophagus below anastomosis

Group 1 showed significantly higher rates of serious esophageal dysfunction compared to Group 2, p=.044
<table>
<tr><th></th><th>Long Gap 6</th><th>Non Long Gap 9</th></tr>
<tr><td>Normal ETT (%)</td><td>0</td><td>0</td></tr>
<tr><td>Minor Dysfunction (%)</td><td>3 (50)</td><td>9 (100)</td></tr>
<tr><td>Major Dysfunction (%)</td><td>3 (50)</td><td>0</td></tr>
</table>
</td>
<td>Majority of EA patients showed excellent clinical scores at midterm follow up with no differences between long gap and non long gap EA

All patients had abnormal ETT and a third had delayed gastric emptying time

Physiologically significant motility disorder (esophagogastric dysmotility) occur more in long gap EA

No relationship between severity of symptoms and gap length

No relationship between severity of symptoms and presence or severity of esophagogastric dysmotility. Symptoms are unreliable in judging severity of dysmotility

Clinical relevance of abnormal motor patterns in patients with absence of symptoms is unclear

Normal values for esophageal transit time and gastric t ½ not known in children hence adult values were used</td>
</tr>
</table>

				Overall ETT duration in Group 1 was significantly longer than Group 2 Delayed gastric emptying (>85min) occurred in 3/6 (50%) in Group 1 vs 2/9 (22.2%) in Group 2 Median t1/2 for Group 1 85min (52.6-227.5) vs 73.7 (54.9-130.5) for Group 2 was not significantly different, p>.05 Esophagogastric dysmotility grades for Group 1 (median 2.5 (1-4) were more severe than Group 2 median 1 (1-2), p>.05 Grades of 4 were seen in 2 Type A, EA	

Table 1 Scores and clinical description of symptom severity of weighed factors

Score	Clinical description
0	Asymptomatic, eats everything, absence of symptoms
1	Minimally symptomatic, infrequent symptoms (occasional) with no negative impact on lifestyle
2	Mildly symptomatic, infrequent symptoms with lifestyle affected, i.e.: one urgent hospital food disimpactation; or one episode of chest infection requiring hospitalization; or well-controlled symptoms, i.e. gastroesophageal reflux managed by medical treatment
3	Severe symptoms, exclusive feeding by gastrostomy tube or severe symptoms related to gastroesophageal reflux such as stricture, two or more hospitalizations for chest infection; or poor weight gain

Table 2 Grades and description of scintigraphic findings used to classify esophagogastric dysmotility

Grade	Clinical description
0	Normal, ETT < 18 s and no $t_{1/2}$ delay
1	Mild, ETT ≥ 18 s and ≤ 5 min.; or $t_{1/2}$ > 85 min.
2	Moderate, ETT ≥ 18 s and ≤ 5 min. and $t_{1/2}$ > 85 min.
3	Marked, ETT > 5 min. alone
4	Severe, ETT > 5 min. and $t_{1/2}$ > 85 min.

ETT, Esophageal transit time: < 18 s: normal: ≥ 18 s and ≤ 5 min.: minor dysfunction, > 5 min.: major dysfunction, half gastric emptying time ($t_{1/2}$) > 85 min.: delayed gastric emptying.

Author/Year	Study Type	Number of Patients Patient Characteristics	Outcomes	Conclusion
Levin et al 2011 (37)	Retrospective cohort study 1987-2006	47 EA patients who had fundoplication 31 (66%) had partial fundoplication (18 Toupet, 5 Thal and 8 other) Median follow up 4.52yrs (1-17.8) 16 (34%) had complete fundoplication (Nissen) Median follow up 6.3yrs (2.5-16.9), p=.39 There was no significant difference between both groups in sex, gestational age, BW, congenital syndromes/associations, type of EA, incidence of post EA repair complications and mean age of fundoplication (1.25yrs). Concomitant gastrostomy placement was also similar More patients in complete fundoplication group had a hiatal hernia repair (23% vs 69%, p=.004) Incidence of pre fundoplication symptoms and contrast study findings were similar in both groups apart from aspiration pneumonia which was more common in the complete fundoplication group. Pre operative dysphagia was commoner in the partial fundoplication group	Table 3 and 4 There were no statistically significant associations between type of operation and symptoms after fundoplication More patients who had partial fundoplication were symptom free without anti reflux medication at time of review (52% vs 13%, p=.012) There was no significant difference in number of patients requiring redo fundoplication between both groups (19% partial fundoplication vs 13% complete fundoplication, p=.0.7)	First study to compare short term outcomes and symptomatology following partial and complete fundoplication in EA patients Data suggests that partial fundoplication is associated with a greater likelihood of symptom and medication free recovery than complete fundoplication in EA-TEF patients

Table 3 Symptoms, complications, and diagnostic imaging pre- and postfundoplication

	Partial		Complete		*P* value [a]
	Preop	Postop	Preop	Postop	
GERD symptoms, n (%)					
Heartburn	0 (0)	1 (3)	0 (0)	1 (6)	–
Vomiting	15 (48)	12 (39)	8 (50)	5 (31)	1.00
Nocturnal cough	6 (19)	10 (32)	4 (25)	3 (19)	.72
Aspiration/ pneumonia	13 (42)	13 (42)	11 (69)	6 (37.5)	.09
Poor weight gain	7 (23)	6 (19)	3 (19)	3 (19)	1.00
Cyanotic episode(s)	12 (45)	5 (16)	5 (31)	0 (0)	.53
Fundoplication complications, n (%)					
Regurgitation	3 (10)	6 (19)	2 (13)	4 (25)	1.00
Dysphagia	6 (19)	14 (45)	0 (0)	6 (38)	.08
Retching	1 (3)	3 (10)	1 (6)	4 (25)	1.00
Diarrhea	2 (6)	3 (10)	0 (0)	2 (13)	.54
Upper GI findings, n (%)					
Hiatus hernia	5 (16)	4 (13)	5 (31)	5 (31)	.27
Stricture	11 (35)	5 (16)	3 (19)	3 (19)	.32
Evidence of reflux	24 (77)	11 (35)	14 (88)	2 (13)	.70

Preop indicates preoperative; Postop, postoperative; GERD, gastro-esophageal reflux disease: GI, gastrointestinal.

[a] *P* value compares the incidence of the symptom preoperatively between the groups.

Table 4 Binary logistic analysis of the effect of fundoplication type on symptom changes following surgery

	Odds ratio	*P* value	95% CI for OR	
			Lower	Upper
GERD symptoms				
Heartburn	2.00	.63	0.12	34.24
Vomiting	0.72	.62	0.20	2.60
Nocturnal cough	0.45	.30	0.10	2.01
Aspiration/pneumonia	0.80	.72	0.22	2.87
Poor weight gain	1.00	1.00	0.21	4.72
Cyanotic episode(s)	0.00	1.00	0.00	∞
Fundoplication complications				
Regurgitation	1.39	.65	0.33	5.89
Dysphagia	0.90	.87	0.25	3.27
Retching	3.01	.20	0.56	16.07
Diarrhea	1.24	.83	0.19	8.31
Upper GI findings				
Hiatus hernia	2.60	.23	0.55	12.24
Stricture	2.43	.37	0.35	17.04
Evidence of reflux	0.20	.06	0.04	1.08

CI indicates confidence interval; OR, odds ratio.

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	GER Dysphagia	Endoscopy	Conclusion
Krug et al 1999 (38)	Prospective cohort study 1971-1978	39 EA patients 11M, 28F 18-26yrs	26/39 (67%) had no GER symptoms 8 had 1 or more symptoms weekly 4 had weekly to daily symptoms 1 had severe therapy resistant symptoms No significant differences in male/female ration, age, alcohol or cigarette use, BMI, perioperative complications between those with and without GER symptoms Follow up was longer in reflux group (40 vs 30mths) 9/39 (23%) had no dysphagia The patients without dysphagia also had no GER symptoms 9 had occasional dysphagia without needing to take precautions 13 had dysphagia and avoided certain foods 8 ate slowly or had extra drink at meal times	34 had endoscopy 2 independent pathologist scored histology Esophagitis scored according to Riddell and Ismail-Beigi Barrett's defined as specialized intestinal metaplasia No strictures seen 6 small diverticulum 6 small hiatal hernia 1 large hiatal hernia Macroscopic appearance 26 Normal 8 had esophagitis (no erosions) 6 Grade 1 1 Grade 2 1 Grade 1 + gastritis 2 Barrett's 3 of this 8 (38%) had no GER symptoms Patient with Grade 2 and 1 with gastritis also had macroscopic Barrett's Histology Biopsies taken from 9 with normal endoscopy and 8 who showed esophagitis/Barrett's Riddell 1 Normal 9 Grade 1 esophagitis 7 Grade 2 esophagitis 2 Barrett's (IM) no dysplasia Histological evidence of esophagitis in 8 in whom endoscopy was normal 4 Grade 1 from endoscopy were Grade 2 on histology Ismael-Beigi 8 Normal 9 Grade 1 esophagitis 1 normal endoscopy had esophagitis on histology If endoscopy had been done only in those with GER symptoms would have missed 6 Grade 1 esophagitis and 2 Grade 2 (Riddell) and gastric metaplasia 1	Incidence of GER symptoms is higher than general population (33% vs 10%, p<.01) Incidence of esophagitis (Riddell) 16/34 (47%) is higher than general population (2%) Incidence of esophagitis (Ismail-Beigi) 9/34 (26%) is higher than general population (2%), p<.01 Poor correlation between symptoms and endoscopic and histological abnormalities Endoscopic and histological findings did not correlate well 2/34 had histologically proven Barrett's which is significantly higher than general population, p<.001 ½ had only mild GER symptoms Advisable to perform endoscopy with biopsies in all adult EA patients

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	GER Symptoms pH Metry/Endoscopy	GER Treatment Medication/Fundoplication (ARS)	Conclusion
Koivusalo et al 2007 (39)	Prospective cohort study 1989-2004	61 consecutive EA patients Spitz classification Type I 47 (77%0 Type II 12 (20%) Type III 2 (3%) Long Gap 8 (13.1%) Significant tracheomalacia requiring aortopexy 6 (9.8%) Significant heart disease 11 (18.3%) Gastric outlet obstruction 10 (16.4%) Duodenal Atresia 6 Hypertrophic Pyloric Stenosis 4 Anastomotic leak 3 Recurrent TEF 1 pH metry and endoscopy done <1yr Endoscopy at 3, 5, 10yrs post repair pH Metry repeated as indicated **pH Metry considered abnormal if:** Overall Reflux Index >10% Or Pre Prandial Reflux Index (excluding 120min after every meal) >5% with/without prolonged reflux episodes >5min Histology graded according to Hetzel **Significant GER (sGER) criteria:** 1) Clinical symptoms required ARS irrespective of results of pH Metry or endoscopy OR 2) Moderate Esophagitis 3) pH Metry abnormal irrespective of symptoms Incidence of sGER recorded at 6mths/1yr/3yr/5yr/10yr post repair	sGER in 28/61 (45.9%) **At 6months** 10/61 (16.3%) had sGER All had ARS for symptoms of Apnea/cyanotic spells with strictures 6 Apnea/cyanotic spells without strictures 4 pH metry confirmed sGER 5/10 5/10 also had aortopexy **1year** 24/61 (39.3%) had sGER 14/24 were new cases of sGER Detected by endoscopic biopsy 4 By pH Metry 6 Both biopsy + pH Metry 4 **3years** 23/52 (44.2%) had sGER 4/23 (17.4%) were new cases of sGER Detected by biopsy 2 By pH Metry 2 **5years** 22/43 (51.2%) had sGER 1/22 (9%) new case of sGER detected by pH Metry **10years** 12/27 (44.4%) had sGER No new cases of sGER Most of sGER patients were symptomatic Resolving sGER 1 (between 5-10yrs) Biopsy returned to normal	At last follow up 14/61 (23%) had used medication 12/14 had sGER 2/14 had no sGER 3/14 had prior ARS 47/61 (77%) had no medication 16/47 had sGER 15/16 had prior ARS 1/16 had no prior ARS 30/47 no sGER 1/47 sGER had resolved 18/61 (29.5%) had ARS 18/28 (64.3% of sGER had ARS 10 had ARS <6mths 2 between 6mths-1yr 5 between 1-3yrs 1 between 5-10yrs 3/17 (18%) who had ARS needed medication because of recurring symptoms or worsening histology Logistic regression analysis for risk of sGER at 6 months and 1 year, long Gap was the only statistically significant factor At 1yr 7/8 patients with LG vs 17/53 without LG had sGER, p<.05 Spitz classification, heart disease, gastric outlet obstruction, tracheomalacia, anastomotic leakage were not significant independent risk factors for sGER	Number of children with sGER doubled from 6 months to 1 year. Incidence of GER increases up to 50% during 5 years follow up. Patients with an existing GER show worsening of esophageal histology. Endoscopic and pH Metric follow up all patients up to 5 years of age seems justifiable. Follow up of patients with sGER should continue longer. Patients with prior ARS should also have follow up due to high rate of failure of ARS to control GER and esophagitis Tracheomalacia probably contributed to some of the apnea/cyanosis <6mths as these patients also needed aortopexy 60% of new cases of sGER occurred during first year. Most continued to have sGER. New cases of sGER can occur at least 5 years post repair Spontaneous resolution of sGER is rare

		sGER considered as resolved if pH Metry/biopsies returned to normal without need for ARS/medications and patient asymptomatic for at least 3yrs Relative Risk for sGER in relation to Spitz classification, heart disease, gastric outlet obstruction, tracheomalacia, anastomotic leakage and long gap was estimated Median length of follow up 5yrs (1-10) 61 at 6mths 61 at 1 yr 52 at 3 yrs 43 at 5 yrs 27 at 10yrs			

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	GER Symptoms/pH Metry/Endoscopy	GER Outcomes	Conclusion
Koivusalo et al 2004 (40)	Observational retrospective analysis 1980-1997	50 consecutive EA patients Endoscopy between 9-12mths, 2-3yrs, 5yrs, 10yrs 18hour pH metry between 9-12mths **Considered abnormal (PPM)** if: Overall Reflux Index >10% Or Pre Prandial Reflux Index (PRI) (excluding 120min after every meal) >5% OR if 3 prolonged reflux episodes >5min at least 2 hours after a meal (LRP) **GER Outcomes** **Favourable:** No esophagitis Or Mild esophagitis but patient on no treatment for GER **Unfavourable:** Moderate or severe esophagitis OR required ARS Patients assessed according to age groups: <6mths, 6-24mths, >24mths Histology graded according to Hetzel **Exclusion criteria**: Unfavourable GER outcome before pH metry could be done/insufficient data/esophageal reconstruction-40 /90patients excluded Median age 13.1yrs (4.1-23.1) Median BW 2910g (1240-4250) Other GI anomaly 7 Long Gap 6 Upper pouch myotomy 6 Aortopexy 4 Initial pH Metry was done at 9.2mths (2.5-95) Median follow up after pH Metry 59mths (0.3-217.6)	**Overall** Pathologic pHMetry (PPM) 10 RI>10% 6 PRI>5% 2 LRP 2 Normal pH Metry (NPM) 40 **10/50 (20%) had pH metry <6mths** Symptoms Aspiration 3 Stricture 7 7/10 had NPM 3 had PPM In 6 with NPM GER outcome remained favourable after median follow up of 27.8mths (17.1-74) and 3 endoscopies **35 (70%) had pH Metry between 6-24mths** 14/35 had moderate/severe symptoms Stricture 1 Vomiting/dysphagia 7 Respiratory 6 Asymptomatic 21 PPM 6 NPM 29 Endoscopy Moderate esophagitis in 7 Severe esophagitis 2 **5 had pH Metry at >2yrs a**ge Symptomatic 1 (PPM) Asymptomatic 4 (NPM)	**Overall** Of 10 with PPM 9/10 (90%) had unfavourable outcomes 5/40 with NPM (12.5%) had unfavourable outcomes **<6 months age** In 4 patients GER became unfavourable after median follow up of 3.5mths (0.3-9.2) 2 /4(1 NPM and 1 PPM) needed early ARS 2/4 (both PPM) developed moderate esophagitis and needed ARS **6-24 months age** 26 (NPM 25, PPM 1) had favourable outcome Median Follow Up 88.6mths (10.4-217.6) and 3 endoscopies In 9 (PPM 5, NPM 4, symptomatic 7, asymptomatic 2) GER became unfavourable after median follow up of 7.2mths (0.3-111.2) In 7/9 patients with esophagitis (PPM 4, NPM 3) had ARS In 2/9 (NPM 1, PPM 1) an unfavourable outcome seen in third and fourth endoscopy **>2yrs age** Unfavourable outcome 1 . Patient had PPM and respiratory symptoms and had ARS 4 with NPM/asymptomatic had favourable outcomes after median follow up of 83.8mths (61.6-110.3) and 5 (3-5) endoscopies Of total 14 with unfavourable GER outcomes 12 needed ARS Median age at ARS was 16.4mths (3.6-73.1) **Overall** Only 8/12 who required ARS had PPM 4 with NPM had ARS based on symptoms and endoscopy Sensitivity 80% (8/10), specificity (95%) 36/38 and positive predictive value 66% (8/12) of pMetry for predicting need for	In this study first post repair pH Metry was used as a prognostic tool to detect clinically significant GER First post EA repair pH Metry has good specificity and PPV for outcome of EA associated GER. pH Metry only gave 63% sensitivity for unfavourable GER outcome and 66% sensitivity for need for ARS. Specificity was 87.5% but 36% or patients with unfavourable GER were missed. pH Metry in <6moth old babies might have given false negative results due to frequent milk feeds. Omitting endoscopy and clinical follow up on grounds of normal pH Metry is not warranted and may result in complications secondary to GER Recommend screening by pH Metry and endoscopy by 9-12months. Patients with PPM or endoscopic signs of unfavourable GER need further surveillance.

				eventual ARS 9/22 patients with GER symptoms and 1/28 without symptoms had PPM, p>.05 12/22 with GER symptoms and 2/28 without symptoms had unfavourable outcome, p<.05 PPV of pH Metry was high (90%) irrespective of age when first pH Metry was done 5/14 (36%) (1<6mths and 4 between 6-24mths) with unfavourable outcomes were not detected by pH Metry See Tables 2 and 3	

Table 2 GER outcome in relation with pHmetry in 50 EATOF patients

pH monitoring			Outcome of GER		Predictive figures of pH monitoring		
Age			Unfavorable	Favorable	Sensitivity	Specificity	Positive predictive value
< 6 months	Pathologic	3	3	0	75% (3/4)	85.7% (6/7)	100% (3/3)
	Normal	7	1	6			
6–24 months	Pathologic	6	5	1	55.5% (5/9)	86.2% (25/29)	83.3% (5/6)
	Normal	29	4	25			
> 24 months	Pathologic	1	1	0	100% (1/1)	100% (4/4)	100% (1/1)
	Normal	4	0	4			
Total	Pathologic	10	9	1			
	Normal	40	5	35			
	All	50	14	36	64% (9/14)	87.5% (35/40)	90.0% (9/10)

Table 3 Reflux index (*RI*) in relation to favorable and unfavorable GER outcome and need for antireflux procedures (*ARP*), and number of patients with RI > 4%, > 7%, and > 10% (*PRI* preprandial reflux index, *LPR* long reflux periods)

	Pathologic pHmetry	Normal pHmetry	RI median (range)	RI > 4%	RI > 7%	RI > 10%
Favorable GER outcome ($n = 36$)	1 (PRI > 5%)	35	2.0 (0.2–7.6)[a]	11	2	0
Unfavorable GER outcome ($n = 14$)	9 (64%) RI > 10%, $n = 6$ PRI > 5%, $n = 1$ LPR, $n = 2$	5 (36%)	8.0 (0.4–25.7)[a]	11 (79%)	8	6
ARP needed ($n = 12$)	8	4	8.0 (2.1–25.7)[b]	10	7	5
No ARP ($n = 38$)	2	36	2.0 (0.2–11.1)[b]	12	3	1
Median (range) RI	11.0 (4.2–25.7)[c]	2.0 (0.2–7.6)[c]				

[a] RI in patients with pathologic pHmetry vs. normal pHmetry ($p < .05$)
[b] ARP vs no ARP ($p < .05$)
[c] Unfavorable vs. favorable GER outcome ($p < .05$)

Author/Year	Study Type	Number of Patients Patient Characteristics	Results of Electrogastrography	Conclusion
Yagi et al 1997 (41)	Case Control Study	13 EA Patients 9M, 4F Mean 7.6yrs (1-17) All symptomatic 3 Type A, EA 10 Type C, EA 5 Control 1< 4F Mean 8.2yrs (5-11) No GI disorders	The peak spectral frequency (PSF) in EA group was3.31+/-0.778 cpm and 3.43+/-0.504 cpm in fasting and post prandial period respectively The peak spectral frequency (PSF) in control group was 3.14+/-0.331 cpm and 2.99+/-0.303 cpm in fasting and post prandial period respectively, p=NS **Dysrhythmias in 5 EA patients** 2 postprandial 3 l fasting and post prandial GER seen in contrast study in 3/5 (60%) No GER symptoms 2/3 were Type A, EA Mean spectral frequencies (MSFs) of EA patients with dysrhythmias n fasting and post prandial state were 3.97+/-0.896 cpm and 3.79+/-0.588cpm respectively. Mean spectral frequencies (MSFs) of EA patients without dysrhythmias n fasting and post prandial state were 2.90 +/-0.266 cpm and 3.20+/-0.288cpm respectively. The MSFs of the EA patients with dysrhythmias were significantly higher than those without dysrhythmias in both the fasting (p<.01) and postprandial state, (p<.05) There was no significant difference in the MSF between the EA patients without dysrhythmias and the controls The peak spectral frequency variability (PSFV) of the EA patients with dysrhythmias in the fasting and post prandial state was 1.35+/-0.809cpm and 1.97 +/-0.425cpm respectively. The peak spectral frequency variability (PSFV) of the EA patients without dysrhythmias in the fasting and post prandial state were 0.539+/-0.338cpm and 0.629+/-0.263cpm respectively The PSFVs in the EA patients with dysrhythmias was significantly higher than those in the patients without dysrhythmias both in the fasting (p<.05) and the post prandial state (p<.001) There was no significant difference in the PSFVs between EA patients without dysrhythmias and the controls The power ratio (PR) was above 1 in 10(77%) of EA cases and 4 (80%) of controls	The contractile activity in the stomachs of EA patients was lower than controls as shown by the lower PR value Dysrhythmias in the stomach can be seen in even asymptomatic EA patients Dysrhythmias may have a role in functional GI symptoms in EA patients Gastric dysrhythmias in EA patients are a marker of gastric neuromuscular dysfunction and may be congenital and due to loss of intrinsic inhibitory innervation or lack of extrinsic autonomic inhibition Electrogastrography helps us study gastric function in EA patients

			The PR in EA group was 2.62+/-1.73 and that of controls was 7.56 +/- 8.98. The PR in the control group was significantly higher than that in the EA group, p<.05 The PR in the EA patients with dysrhythmias was 2.45+/-1.51 and in those without dysrhythmias was 2.74+/-1.95. The presence of dysrhythmias had no relationship to the PR value	

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Stricture	Tracheomalacia Dying Spells	Recurrent Pneumonia Recurrent TEF	GER	Conclusion
Yang et al 2006 (42)	Retrospective Review 1994-2003	15 EA Patients 8M (53.3%), 7F (46.7%) Mean gestational age 37+/-3.2 (27-41) Mean BW 2491+/-708g (770-3825) 3 Premature infants 5 SGA **EA Types** Type A 1 Type C 12 Type H 1 Tracheal Atresia without fistula 1 **Waterston** Group A 2 Survival 100% Group B 6 Survival 83.3% Group C 7 Survival 14.3% Associated anomalies 12 (80%) Anastomotic Leak 4 (33.3%)	2 (16.7%)	Tracheomalacia (TM) 8 (66.7%) Dying Spell 4 (33.3%) 1/4 also had esophageal stricture 3/8 TM with dying spell had tracheal stent 2/3 with stent died 1 TM + dying spell patient got tracheal balloon dilatations	Recurrent pneumonia 6 (50%) Recurrent TEF 0	GER 6 (50%) 2/6 had strictures 2/6 had fundoplication	Survival rate of EA patients is influenced by associated anomalies and tracheomalacia with dying spells

GER in EA-TEF

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of Patients
Patient Characteristics
Methodology</th><th>Symptom Results
pH-Impedance Results</th><th>Conclusions</th></tr>
<tr>
<td>Frohlich et al
2008 (43)</td>
<td>Prospective case cohort study</td>
<td>24 EA Patients
Median age 3.5 yrs (4mths-23 years)
17M, 7F

EA Type (Vogt)
Type II 1 (4%)
Type IIIb 21 (87.5%)
Type IIIc 1 (4%)Type IV 1 (4%)

GER Questionnaire
Symptoms:
Heartburn/Agitation (infants/toddlers)
Belching
Cough
Regurgitation
Odynophagia
Dysphagia (liquids/solids)

Symptom intensity:
0 Not Present
1 Mild
2 Moderate
3 Severe

Symptom Frequency:
1 = 2-3/month
2= 1/wee
3= 2-3/week
4= Daily

For each symptom
Symptom Score = Intensity X Frequency

Total Symptom Score = Sum of all Symptom Scores

Patients divided into two groups:
Minor Symptoms = Total Symptom Score <14
Major Symptoms= Total symptom Score >14

Impedance Swallow test done in 5 EA Patients
And 6 normal patients with GER symptoms with no prior surgery
EA Patients
Median age 13 years (9-23)
Non EA Patients median age 8-12yrs
10 liquid and 10 viscous swallows</td>
<td>Symptoms:
<table><tr><th></th><th>N</th><th>%</th><th>Number of patients with symptom score >/=4 for a single symptom</th></tr><tr><td>Heartburn</td><td>4</td><td>17</td><td>2</td></tr><tr><td>Belching</td><td>9</td><td>38</td><td>5</td></tr><tr><td>Cough</td><td>14</td><td>58</td><td>9</td></tr><tr><td>Dysphagia for liquids</td><td>3</td><td>13</td><td>2</td></tr><tr><td>Dysphagia for solids</td><td>14</td><td>58</td><td>8</td></tr><tr><td>Odynophagia</td><td>3</td><td>13</td><td>1</td></tr></table>
Median of Total Symptom Score for all Symptoms 7.5 (0-34)
6 patients had no symptoms during study

Impedance:
24 EA Patients had 911RBM
379 (42%) Acidic
532 (58%) Weakly Acidic
Median Bolus Index 1.7% (0.4-12.2)
If take normal for adults as 1.4%, 16 EA patients (67%) had abnormal bolus index

pH Probe:
1073 episodes of pH <4
Median pH RI 2.5% (0-42.3)
8 (33%) had pathological pH (>5%)

No significant correlation between total symptom score and the RI or Bolus Index

Patients with Major Symptoms showed a statistically significant higher RI (18.15% vs 1.95%), p<.05 and Bolus Index (4.5% vs 1.5%), p<.01, patients with Minor Symptoms

201 Symptom Events
85 (42%) were associated with RBM
Number of associated weakly acidic refluxes (55, 26%)were greater than number of associated acidic refluxes (35, 16%)

MII-pH increased the SI in pooled data from 14% to 36%
The SI for non acid reflux events was 22%</td>
<td>Half of GER events could only be detected by MII

Pathological RI was seen in 33% with PH, whereas a bolus index above normal values for adults was seen in 67% of patients.

More than half 58% of reflux events detected were weakly acidic and would not have been detected by pH probe alone. Sensitivity of pH monitoring alone was only 42%. Only 35% of episodes detected by pH monitoring were confirmed by MII

Results for EA patients were negative except for SSI for non acid reflux events. This could be due to lack of sensitivity and ability to communicate symptoms in EA group.

No correlation between overall symptom score and RI or Bolus Index. No association between specific symptoms and reflux events. Statistically significant correlation with a higher RI and bolus index was seen in patients with “Major Symptoms”

EA patients with GER rarely describe typical GER symptoms like heartburn.

Weakly acidic reflux showed a higher tendency to be related to symptoms than did acid reflux, especially with regard to post prandially reflux.

37% of reflux events migrated proximally. There was no relevant correlation of high reflux events and respiratory symptoms.

Impedance swallowing test showed impaired bolus transit in distal esophagus in all EA patients

Lower impedance amplitude in distal channels could be due to esophageal hypomotility and liquid (saliva+refluxate) resting against the wall in the distal esophagus

Role of weakly acidic relux in EA patients remains to be determined.

Even patients with no symptoms/few symptoms may have severe GER</td>
</tr>
</table>

			No difference in the SSI using pH/MII (9.88%) vs pH Probe alone (9.2%) The SSI for non acid reflux events was 10.36% By definition only the SSI for non acid reflux events could be considered positive Of the 911 reflux events, 90 (9.9%) were associated with a symptom event perceived by the patients No difference between acidic and weakly acidic reflux episodes See Table 2 **Proximal Migration:** 36.8% of all refluxes migrated proximally Of these high refluxes, 47% were weakly acidic and 53% were acidic 4 patients showed >50% high refluxes 1 was asymptomatic 3 had respiratory symptoms No correlation between amount of high refluxes and symptom scores or RI Impedance Swallowing Test: The 5 EA patients tested did not stand out with regard to total symptom score (median 7, range 0-10), RI (median 9, range 2.2-17.7) or bolus index (median 1.5, range 0.6-1.8) The non EA patients showed MII and pH data no different from the EA group with regard to symptom score (median 4.5, range 0-36), RI (median 6.65, range 2-28.9), or bolus index (median 1.65, range 1.1-3) In EA Group less than half of all swallows showed a complete bolus transit unlike the non EA group. The EA group had normal pattern of bolus entry and exit in the proximal channels but in the distal channels there was uncoordinated pattern of bolus entry and exit. There was significant difference in impedance baseline amplitude in channels 5 and 6 in EA and non EA patients. The baseline of EA patients was 25% of the control group values, unlike in the proximal channels.	

TABLE 2. *Total symptom events in 24 patients and their association to reflux events in general and divided into acidic and weakly acidic reflux events as detected by combined MII and pH measurement*

		Reflux-associated symptoms		Acidic reflux-associated symptoms		Weakly acidic reflux-associated symptoms	
Symptoms	Combined number of symptom events of all measurements	Events recorded	%	Events recorded	%	Events recorded	%
Heartburn	22	4	18	0	0	4	18
Agitation	20	13	65	8	40	5	25
Cough	147	57	39	19	13	38	26
Regurgitation	12	11	92	6	50	5	42
Total	201	85	42	33	16	52	26

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Contrast Study	Anastomotic Leak	GER	Stricture	Recurrent TEF	Conclusion
Yanchar et al 2001 (44)	Retrospective Review Between 1989-1999	111 EA patients 101 were Type C, EA 90 had repairs Mean gestational age 38.1wks (30-42) 51% Males 37% VACTERL 32% cardian anomalies Mean weight at repair 2.7Kg (1.1-4.2)	87 had it done in early post-operative period Median time of study 9.1 days post op (2-23) before consideration of oral feeding **Results of study shown in Table 2**	Seen in 15 Clinical Leaks 6 Radiological Leaks 9 **Factors associated with development of anastomotic leas shown in Table 3**	Seen in 4/87 (46%) who had follow up 11 had medical therapy 29 had fundoplication **Factors associated with development of GER shown in Table 4**	Seen in 15 (17%) All responded to dilatations except 1 who needed resection. **Factors associated with development of stricture shown in Table 5**	Seen in 3 and 1 missed fistula 1 was associated with previous major leak. None associated with a radiological leak None of these fistulae were seen in initial post-operative contrast study	Early and late complications after EA repair can be identified and anticipated based on clinical findings at time of repair and during post-operative period. The use of early routine contrast studies with no clinical suspicion of a complication has little value in terms of predicting complications or future clinical course Contrast studies should be selectively done in patients with moderate or severe anastomotic tension or those who had myotomies and in those with clinical evidence to suggest a complication.

Table 2. Upper GI Studies: Techniques and Findings

Technique of Study	No. of Patients (%)
Barium (versus water-soluble) contrast (69)*	38 (55)
Patient swallowed contrast (70)	64 (91)
Transanastomotic tube in situ (70)	34 (49)
Finding	
Esophageal shortening (63)	29 (46)
Decreased esophageal motility (49)	40 (82)
Anastomotic appearance (70)	
Narrowing	52 (74)
Smooth/tapered narrowing, length < 1 vertebral body height	17
Smooth/tapered narrowing, length > 1 vertebral body height	29
Abrupt narrowing	4
Narrowing not otherwise specified	2
No/minimal narrowing	18 (25)
Anastomotic index (51)†	mean 0.52 (range, 0.12 to 1.0)
Leak (87)	15 (17)
Radiologic	9
Minor	1
Major	5
GER (58)	31 (53)
Reflux to Upper (versus Lower) half of esophagus	8
Major (versus Minor or no) reflux	16

* Number of patients for whom these data are available is indicated in parentheses.

† Anastomotic index = ratio of maximum diameter of anastomosis to maximum diameter of upper esophageal pouch.

Table 3. Factors Associated with Development of Anastomotic Leak

Variable	Clinical Leaks (n = 6)		Radiologic Leaks (n = 9)
	Odds Ratio (95% CI)		
Patient characteristics			
Gestational age	NS		NS
Weight at time of surgery	NS		NS
VACTERL association	NS		NS
Associated cardiac anomaly	NS		NS
Intraoperative factors			
Silk (versus absorbable) suture	1.0 (0.2-5.8)		**~0*†**
Suture size	NS		NS
Transanastomotic tube	NS		NS
Chest tube	NS		NS
Esophageal tear (repaired in operating room)	NS		NS
Increasing tension scale	**14.4 (1.4-148)**	**15.7 (1.3-187)**‡	0.6 (0.2-1.6)
Use of myotomies	**16.8 (1.04-271)**	NS‡	NS
Early postoperative factors			
Pneumothorax (de novo)	**41.5 (3.1-560)**		~0
Suspicion of leak	∞§		~0
Transanastomotic tube feeds	NS		NS

Abbreviation: NS, not statistically significant.

* Bold type indicates statistically significant, with OR not spanning 1.

† Because no radiologic leaks occurred with silk sutures, the OR approaches 0.

‡ Multivariate analysis including both variables of tension and myotomies.

§ Because all clinical leaks were suspected before confirmation, the OR approaches infinity.

Table 4. Factors Associated with Development of Gastroesophageal Reflux

Variable	GER (n = 40)	GER Medically Treated (n = 11)	GER Surgically Treated (n = 29)
	Odds Ratio (95% CI)		
Patient characteristics			
Gestational age	NS	NS	NS
Weight at time of surgery	NS	NS	NS
VACTERL association	NS	NS	NS
Cardiac anomaly association	**0.3 (0.1-0.7)**	0.4 (0.1-2.1)	**0.3 (0.1-0.9)**
Intraoperative factors			
Transanastomotic tube placed	NS	NS	NS
Increasing tension scale	**1.9 (1.01-3.4)***	1.1 (0.5-2.7)	1.8 (0.96-3.4)
Use of myotomies	NS	NS	NS
UGI findings			
Esophageal shortening	NS	NS	NS
Diminished esophageal motility	NS	NS	NS
Reflux of contrast	NS	NS	NS
Reflux to upper (versus lower) half of esophagus	NS	NS	NS
Major reflux (versus none or minor)	NS	NS	NS

Abbreviation: NS, not statistically significant.

* Bold type indicates statistically significant, with OR not spanning one.

Table 5. Factors Associated With the Development of a Stricture

Variable	Odds Ratio (95% CI)
Patient Characteristics	
Gestational age	NS
Weight at time of surgery	NS
VACTERL association	NS
Cardiac anomaly association	NS
Intraoperative factors	
Suture type (silk versus absorbable)	NS
Transanastomotic tube	NS
Chest tube	NS
Tension scale (0-3)	NS
Use of myotomies	NS
UGI findings	
Esophageal shortening	NS
Diminished esophageal motility	NS
Presence of anastomotic narrowing (any form)	NS
Smooth vs. abrupt/shelflike narrowing	NS
Length of narrowing (versus height of adjacent vertebral body)	NS
Anastomotic index	NS
Reflux of contrast	NS
Reflux to upper half of esophagus	NS
Major reflux (versus none or minor)	NS
Postoperative clinical course	
Leak (any)	1.9 (0.5-7.3)
Clinical leak	3.3 (0.5-21.5)
Radiologic leak	1.3 (0.2-7.1)
GER	**4.1 (1.2-14.1)***
GER with medical management	2.0 (0.5-8.6)
GER requiring surgical management	2.8 (0.9-8.6)

Abbreviation: Not statistically significant.

* Bold type indicates statistically significant, with OR not spanning 1.

GER in EA-TEF

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of Patients
Patient Characteristics
Methodology</th><th>GER</th><th>GER Therapy
Medication/Anti Reflux Surgery</th><th>Conclusion</th></tr>
<tr>
<td>Koch et al
1986 (45)</td>
<td>Retrospective and Prospective case cohort study</td>
<td>
3 Groups of patients
<table>
<tr><th>Group</th><th>Patients n</th><th>Period Of Primary Repair</th><th>Follow Up (years)</th></tr>
<tr><td>I</td><td>27</td><td>1951-1958</td><td>16-23</td></tr>
<tr><td>II</td><td>28</td><td>1970-1979</td><td>4-14</td></tr>
<tr><td>III</td><td>12</td><td>1979-1982</td><td>1.5-5</td></tr>
</table>
Group I were operated elsewhere followed up clinically, radiologically, manometrically and majority (23) endoscopically (Retrospective Study)

Group II were operated at authors center, prospectively followed up clinically, radiologically at 3-6month intervals initially then 12-24monthly. 12.28 had endoscopy. 7/28 had manometry

Group III were also followed up prospectively clinically, radiologically, endoscopically and also with pH Metry

Anastomotic Complications
<table>
<tr><th>Complications</th><th>I</th><th>II</th><th>III</th></tr>
<tr><td>Recurrent TEF</td><td>1/27</td><td>3/28</td><td>1/12</td></tr>
<tr><td>Anastomotic Stricture</td><td>14/27</td><td>12/28</td><td>3/12</td></tr>
<tr><td>Dilatation < x2</td><td>14</td><td>8</td><td>3</td></tr>
<tr><td>Resection</td><td>-</td><td>4</td><td>-</td></tr>
</table>
</td>
<td>
Characteristics of Pathological GER

Symptoms
Regurgitation of gastric contents >3 x /24Hr
Failure to thrive
Recurrent aspiration
Epigastric or retrosternal pain

Barium Swallow
Spontaneous and repeated reflux into lower esophagus
Fixed hiatal hernia

Esophagoscopy
Esophagitis (erythema/erosion)
Stricture
Endobrachyesophagus

Manometry
Resting LES pressure </= 12mmHg
Common cavity phenomenon spontaneously or on abdominal compression
In group I hormonal stimulation of LES was done with IV Pentsgastrin

pH Metry
Total Reflux >4%
Reflux duration during sleep >1.5% of measuring time

Pathological GER
<table>
<tr><th>Diagnosis</th><th>I</th><th>II</th><th>III</th></tr>
<tr><td>Symptoms</td><td>0/27</td><td>9/28</td><td>4/12</td></tr>
<tr><td>Barium</td><td>0/27</td><td>16/28</td><td>8/12</td></tr>
<tr><td>Esophagoscopy</td><td>2/23</td><td>6/28</td><td>1/12</td></tr>
<tr><td>Manometry</td><td>6/27</td><td>2/7</td><td>0/12</td></tr>
<tr><td>pH Metry</td><td>-</td><td>-</td><td>3/12</td></tr>
<tr><td>Found in</td><td>7/27</td><td>21/28</td><td>9/12</td></tr>
</table>
Number and combination of pathological reflux findings in various age groups Table 5

75% of oldest group had no pathological signs of GER vs 75% of youngest group who had pathological signs of GER

Most pathological findings were by radiology followed by symptoms
</td>
<td>
Evolution of prospectively controlled GER on medical therapy
<table>
<tr><th>Group</th><th>n</th><th>Number Of Normalisations (after)</th><th>Number Of Improvements (after)</th></tr>
<tr><td>II</td><td>11</td><td>6 (1year)</td><td>-</td></tr>
<tr><td></td><td></td><td>5 (4-9 years)</td><td>-</td></tr>
<tr><td>III</td><td>8</td><td>4 (1 year)</td><td>2 (1 year)</td></tr>
<tr><td></td><td></td><td>2 (2 years)</td><td>-</td></tr>
</table>
Indications for anti reflux surgery (ARS)
<table>
<tr><th>Indication</th><th>I</th><th>II</th><th>III</th></tr>
<tr><td>Radiology + Clinical</td><td>-</td><td>5</td><td>-</td></tr>
<tr><td>Radiology</td><td>-</td><td>1</td><td>-</td></tr>
<tr><td>Endoscopy + Radiology</td><td>-</td><td>2</td><td>-</td></tr>
<tr><td>Endoscopy + Clinical</td><td>-</td><td>2</td><td>1</td></tr>
<tr><td></td><td>0/27</td><td>10/28</td><td>1/12</td></tr>
</table>
With exception of 2 cases (cerebral palsy and delayed endoscopy) all ARS were done during first year of life, especially first 4 months. Nissen fundoplication was done in all

ARS related to early anastomotic complications
<table>
<tr><th>Complications</th><th>n</th><th>I</th><th>II</th><th>III</th></tr>
<tr><td>Recurrent TEF</td><td>5</td><td>-</td><td>2</td><td>1</td></tr>
<tr><td>Anastomotic Stricture</td><td>29</td><td>-</td><td>3</td><td>-</td></tr>
<tr><td>Dilatations >2x</td><td>25</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Resection</td><td>4</td><td>-</td><td>3</td><td>-</td></tr>
</table>
</td>
<td>
Pathological reflux seen in one quarter of patients aged 16-23 years and three quarters of those aged 1.5-14 years.

Manometry diagnosed pathological GER in older patients, radiology was most decisive in younger patients

Strong tendency for anastomotic complications (recurrent TEF and stricture requiring resection) to manifest as pathological GER, requiring ARS, hence these patients should closely followed up

Need for medical or surgical therapy for GER is decided on almost exclusively in first year of life

GER diagnosed beyond the first year is seldom of clinical significance

According to authors follow up of 1.5-14 years of 19 conservatively treated patients majority of whom showed normalization of pathological GER within 1 year disproves assumption that GER in EA does not improve

Factors influencing the incidence of GER in EA patients were:

1.Definition of GER based on diagnostic method used

2. Patients age at diagnosis of GER

3. Anastomotic complications requiring a second operation
</td>
</tr>
</table>

Table 5. Number and combination of pathological reflux findings after primary repair of esophageal atresia in various age groups

No. of pathological findings	Group		
	I	II	III
1	6 (5 × mano) (1 x endo)	11 (7 × rx) (3 × clin) (1 × mano)	3 (3 × rx)
2	1 (1 × endo + mano)	8 (4 × rx + clin) (3 × rx + endo) (1 × clin + endo)	5 (2 × rx + clin) (2 × rx + pH-metr) (1 × clin + pH-metr)
3	–	2 (1 × rx + clin + endo) (1 × rx + endo + mano)	1 (1 × rx + clin + endo)
Total	7/27	21/28	9/12

clin = clinical; rx = radiological; endo = endoscopic; mano = manometrical; pH-metr = pH monitoring

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Stricture	GER	Conclusion
Morabito et al 2006 (46)	Retrospective Review Between 1984-2004	67 EA patients 54 with distal fistula (Vogt Type III) were studied Median weight 2.7Kg Median gestational age 36.1 weeks VACTERL 4 CHARGE2 Cardiac 3 Severe tracheobronchomalacia 1 All patients had upper pouch tailoring and lower pouch flap augmentation for reconstruction of their esophagus with a wide oblique anastomosis Anastomotic Leak 11 (16%) Conservative management Recurrent TEF 5 (7.5%) Follow up from 1-16 years All had normal growth (weight and height centiles) and mental development except for the child with CHARGE	Dilatation only done in those with clinical dysphagia and proven stricture Stricture 2 (3%) Both did not respond to dilatations and needed redoanastomosis	Investigation for GER only done in those with: Vomiting Failure to thrive Retrosternal/epigastric pain Recurrent chest infection 7 (13%) had clinically significant GER This was confirmed on: pH Metry Endoscopy Contrast swallow 2 responded to m medications 4 had anti reflux surgery (3 Nissen, 1 Thal) for vomiting/respiratory complication and failure to thrive 1 with associated cardiac condition got a gastrostomy	Lower than expected incidence of clinically significant GER, according to authors was due to decreased traction on the distal esophagus, preservation of vagi and vascular supply of esophageal pouch. Clinically significant GER is not inevitable post EA repair and not all children need ARS Authors also believe that upper pouch tailoring and lower pouch augmentation led to uniform wider caliber of the esophagus which led to reduced rate of stricture development and need for dilatation. They saw no clinical or radiological evidence of anti peristaltic effect of inverted upper pouch flap.

GER in EA-TEF

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of Patients
Patient Characteristics</th><th>Investigations</th></tr>
<tr>
<td>Holschneider et al
2007 (47)</td>
<td>Retrospective Review
Between
1993-2005</td>
<td>
Patient population undergoing fundoplication

Table 1 Patient population undergoing fundoplication
<table>
<tr><th></th><th>Total</th><th>Esophageal atresia</th><th>Other</th></tr>
<tr><td>Patients (n)</td><td>148</td><td>87</td><td>61</td></tr>
<tr><td>Surgery for recurrence</td><td>10</td><td>8</td><td>2</td></tr>
<tr><td>Relapse</td><td>18</td><td>14</td><td>4</td></tr>
<tr><td>Male</td><td>89</td><td>56</td><td>33</td></tr>
<tr><td>Female</td><td>59</td><td>31</td><td>28</td></tr>
<tr><td>Age at operation</td><td>3.6
(1 mo – 16 yrs)</td><td>3.4
(1 mo – 14 yrs)</td><td>3.9
(1 mo – 16 yrs)</td></tr>
<tr><td>Follow-up period</td><td>3.7
(1 mo – 10 yrs)</td><td>4.3
(1 mo – 10 yrs)</td><td>3.6
(3 mo – 12 yrs)</td></tr>
<tr><td>Died</td><td>11</td><td>8</td><td>3</td></tr>
</table>
</td>
<td>
Incidence of pathological findings in the preoperative investigations

Table 2 Incidence of pathological findings in the preoperative diagnosis
<table>
<tr><th></th><th>Evaluations total</th><th>Patholog. findings</th><th>EA total</th><th>EA pathol.</th><th>Others total</th><th>Others pathol.</th></tr>
<tr><td>Pathological pH-metry</td><td>121</td><td>112 (92.5%)</td><td>70</td><td>66 (94.2%)</td><td>51</td><td>46 (90.2%)</td></tr>
<tr><td>Esophagitis</td><td>97</td><td>93 (95.8%)</td><td>54</td><td>51 (94.4%)</td><td>43</td><td>42 (90.6%)</td></tr>
<tr><td>Pathological sonography</td><td>89</td><td>57 (64%)</td><td>46</td><td>25 (54.3%)</td><td>43</td><td>32 (74.4%)</td></tr>
<tr><td>Pathological X-ray</td><td>142</td><td>129 (90.8%)</td><td>83</td><td>74 (89.1%)</td><td>59</td><td>55 (93.3%)</td></tr>
<tr><td>Axial hernia*</td><td>146</td><td>72 (49.3%)</td><td>85</td><td>36 (42.3%)</td><td>61</td><td>36 (59%)</td></tr>
</table>
* including paraesophageal hernia
</td>
</tr>
</table>

Fundoplication Procedure Types

Table 3 Operative procedures used in 148 patients of the patient population

	Total (n = 148)	Esophageal atresia (n = 87)	Other (n = 61)
Nissen	126	71	55
of which with a double-row cuff	79	53	26
Thal	12	7	5
Boix-Ochoa	2	2	0
Only hiatusplasty	1	0	1
Technique unknown	7	7	0

Table 4 Operative procedures used in the comparison group ("Other")

	Retarded (n = 30)	Primary reflux (n = 23)	Relevant previous operations* (n = 8)
Nissen	28	19	8
of which with a double-row cuff	16	6	4
Thal	1	4	0
Boix-Ochoa	0	0	0
Only hiatusplasty	1	0	0
Technique unknown	0	0	0

* diaphragm operations, gastric operations

Intra an d Postoperative Complications

Table 5 Intra- and postoperative complications

	Total (n = 148)	Esophageal atresia (n = 87)	Other (n = 61)
Intraoperative complications	5 (3.8%)	4 (4.6%)	1 (1.6%)
Postoperative complications	14 (9.5%)	9 (10.3%)	5 (8.2%)
Died postoperatively	1 (0.7%)	0	1 (1.6%)

Reflux Recurrence and Dysphagia

Table 6 Postoperative reflux recurrence and dysphagia in the total patient population (n = 148)

	Total (n = 148)	Esophageal atresia (n = 87)	Other (n = 61)
Recurrence	18 (12.2%)	14 (16.1%)	4 (6.5%)
Operations for recurrence	10 (6.7%)	8 (6.9%)	2 (3.2%)
Dysphagia/stenosis	19 (12.8%)	15 (17.2%)	4 (6.5%)
Dumping	17 (11.5%)	16 (18.3%)	1 (1.6%)

Table 7 Reflux recurrence and dysphagia in patients without esophageal atresia (n = 61)

	Retarded without EA (n = 30)	Primary reflux (n = 23)	Relevant previous operations (n = 8)
Recurrence	3 (10%)	1 (4.3%)	0
Operations for recurrence	2 (6.6%)	0	0
Dysphagia/stenosis	2 (6.6%)	1 (4.3%)	1 (12.5%)
Dumping	0	0	1 (12.5%)

Table 9 Comparison of reflux recurrence and dysphagia with respect to fundoplication technique

	Total of open Nissen (n = 126)	Recurrences (n = 17)	Dysphagia (n = 13)
Double-row Nissen cuff	n = 79	10 (12.6%)	11 (14.0)
Esophageal atresia	n = 53	9 (17.0%)	8 (15.1%)
Other	n = 26	1 (3.8%)	3 (11.5%)
Single-row Nissen cuff	n = 47	7 (14.9%)	2 (4.2%)
Esophageal atresia	n = 18	4 (22.3%)	2 (11.1%)
Other	n = 29	3 (10.3%)	0

GER in EA-TEF

Comparison of Outcomes

Comparison of outcomes of fundoplication in EA patients and GER patients

Table 8 Comparison of the outcomes of operative therapy in patients with esophageal atresia and in patients with GERD without primary disease*

	Total patient population	Esophageal atresia	Primary GERD (without primary disease)
Patients (n)	148	87	23
Age at operation	3.6 (1 mo – 16 yrs)	3.1 (3 mo – 14 yrs)	1.7 (1 mo – 6 yrs)
Follow-up period	3.7 (1 mo – 10 yrs)	4.3 (1 mo– 10 yrs)	4.6 (4 mo – 12 yrs)
Intraop. complications	5	4 (4.6%)	1 (4.3%)
Postop. complications	14	9 (10.3%)	1 (4.3%)
Nissen	126	71	19
Thal	12	7	4
Boix-Ochoa	2	2	0
Other procedures	8	7	0
Recurrence	18 (12.2%)	14 (16.1%)	1 (4.3%)
Reoperation	10 (6.7%)	8 (9.2%)	0
Dysphagia	19 (12.8%)	15 (17.2%)	1 (4.3%)

* excluding patients with mental retardation (n = 30) or patients having undergone previous operations (n = 8)

Conclusion

In EA patients Nissen fundoplication has significantly more complications compared to non EA patients with GERD

The post-operative complications are due to disturbed esophageal and gastric motility in EA patients

There is a higher incidence of Dumping syndrome post fundoplication in EA patients

Long term postoperative follow up is necessary in EA patients until adulthood due to the risk of development of Barrett's esophagus

Table 10 Histological results of 79 esophageal biopsies

Degree of change	I	II	III	IV	Barrett's esoph.	Total
EA	7	13	17	2	1	40
Other	7	16	12	3	1	39

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Results	Conclusion
Nasr et al 2005 (48)	Retrospective Review Between 1977-2003	288 EA Patients 29 (10%) had severe respiratory distress (204+/-330 days of life: Pneumonia Cyanotic episodes/Blue spells Respiratory arrests In the absence of cardiac disease Radiological investigations (Barium Swallow) and endoscopy (gastroscopy/bronchoscopy) confirmed the presence of significant tracheomalacia (TM) and GER in 22 (7.6%) cases. In these cases it was not possible to determine which was the major cause of respiratory distress 7 cases had TM or GER	Decision to proceed with either aortopexy (TM procedure) or fundoplication (FP) was based on the personal preference of the treating surgeon 13 (59%) had initial aortopexy and the respiratory symptoms improved in 7. 6/13 (46%) with persistent respiratory symptoms required a fundoplication within 60+/-36 days of the aortopexy. All patients improved with the second procedure 9/22 (41%) had an initial fundoplication and the respiratory symptoms improved in 6. 3/9 (33%) with persistent respiratory symptoms required an aortopexy within 160+/-176 days after the fundoplication All of the patients improved after the second procedure All 4 groups (TM procedure only, TM procedure followed by FP, FP only, FP followed by TM procedure) were assessed with respect to clinical presentation, associated anomalies, length of time to first and second procedure. There were no significant differences between the groups for any of the parameters	In EA patients with severe respiratory distress it is important to exclude cardiac anomalies and recurrent TEF as these can result in cyanotic spells in addition to TM and severe GER Infants improve after correction of TM as the GER is better handled by non collapsing trachea Similarly it is presumed than infants improve after FP as they are able to breathe better through even a narrow collapsible trachea as long as it is kept clear of gastric contents and not compressed by an esophagus distended by refluxate It is important to realize that irrespective of whether GER or TM is responsible for the severe respiratory distress aortopexy or fundoplication alone may not be successful in 33% and 46% of cases and a second procedure is indicated. With the second procedure all patients had resolution of their symptoms in this study

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Symptoms	Esophageal Ultrasound	Endoscopy & Histology	Manometry	pH Impedance	Predictors for Esophagitis in EA	Conclusion
Pedersen et al 2013 (49)	Prospective case control study	59 EA patients born between 1993-2005 86 were contacted and 59 accepted Participants and non responders were comparable on gender, age, gestational age, BW, type of EA, complications post repair (leak, dilatations) and presence of associated anomalies 25 control patients with GER symptoms were also evaluated EA Median age10.2yrs (7.1-13.3) 32 (54%) M EA patients and controls did not differ significantly on gender, age, gestational age BW was significantly lower for EA	Symptoms enquired about included: Heartburn Regurgitation Use of PPI Eating habits Dysphagia Respiratory symptoms EA 55.9% had symptoms of GERD 69.5% had dysphagia monthly 15.3% had daily dysphagia 55.9% had respiratory symptoms Both dysphagia and respiratory symptoms were more frequent in EA vs controls (p<.0001)	Esophageal wall thickness measured 5cms above cardia and at level of aortic arch EUS completed in 47/59 EA and 24/25 controls EA Mean wall thickness was 3.08+/-0.84mm at 5cms above LES and 2.49+/-0.53mm at level of aortic arch. Esophageal wall thickness did not differ significantly from controls at either level (p=.31 and0.75)	Endoscopic esophagitis classified according to LA classification Biopsies taken from mucosal lesions, and at 5/10/15cms from GE junction Histology graded as mild/moderate/severe. >15 eosinophils/HPF looked for Columnar metaplasia +/- goblet cells and dysplasia commented on Sufficient biopsies taken in 56/59 EA and 24 controls EA 33.9% had LA grade B, C or D esophagitis EA and controls did not differ significantly (p=.15) Mild histological esophagitis seen in 44.1% of EA and 40% controls 9 EA had normal histology and 24 had discrete changes that could not be classified as mild grade esophagitis No significant differences between EA and controls on histological esophagitis or metaplasia 1 EA had gastric and intestinal metaplasia	HREM: Esophageal length LES length LES basal pressure LES residual pressure Hiatal hernia UES basal pressure Swallows categorized as propagating/simultaneous/failed 44 EA patients had full manometry, 7 partial 24 controls had full manometry Esophageal length was significantly shorter in EA vs controls even when corrected for height, p=.02 No differences in UES basal pressure and LES length between groups LES basal pressure was lower in EA (p=.004) No significant differences in distal wave amplitude and presence of hiatal hernia between groups Median % of propagation swallows was 100% for controls and 0% for EA 40/48 (83.3%) of EA had no propagating swallows Only 2 showed >50% propagating swallows Frequency of propagating swallows did not differ between symptomatic and asymptomatic EA patients	53/59 EA had full study 23/25 controls had full study EA RI > 3 in 50 (84.7%) >7 in 32 (54.2%) Median RI 8.3 (4.8-14.9) No significant difference in RI and number of non acidic episodes between EA and controls Controls had significantly higher number of acidic episodes (p=.008) Baseline impedance was significantly lower in EA (716 vs 1314), p<.0001 Baseline impedance in EA with esophagitis (552) was similar to EA without esophagitis (794), p=.22 Baseline impedance in controls with esophagitis (1202)was similar to controls without esophagitis (1322) , p=.32 EA patients and controls with endoscopic esophagitis had a significantly lower baseline impedance (693) vs patients without endoscopic esophagitis (1010), p=.038	**No predictors for endoscopic esophagitis could be found** **Factors looked at included:** GER symptoms Respiratory symptoms Dysphagia Earlier need for dilatation Gender Age Esophageal length corrected for height LES basal pressure LES residual pressure % propagating swallows Histological esophagitis RI	High frequency of GER and respiratory symptoms and dysphagia in EA patients Pathological findings seen in high number of EA patients by endoscopy, manometry and pH impedance No predictors for endoscopic esophagitis in EA patients could be identified Although 55.9% of EA patients had symptoms of GERD, 33.9% had endoscopic esophagitis and 55.2% had RI >7 only 32.2% were on PPI EA patients had severely impaired peristalsis compared to controls. However as endoscopic and histological esophagitis and thickness of esophageal wall and RI was similar in EA patients and controls, impaired peristalsis in EA patients is likely to be due to a congenital anomaly and not esophageal wall inflammation EA patients require routine follow up with endoscopy and pH Metry as 50% had RI>7.

					Eosinophilic esophagitis seen in 6 (10.2%) EA vs 1 (4%) controls, p=.67		Proximal extent of refluxate in EA patients could not be measured as contact to esophageal wall was poor in upper esophagus		However role of HREM in predicting development of esophagitis in EA patients was not shown in this study Eosinophilic esophagitis might be an independent risk factor for dysphagia in EA, in addition to impaired peristalsis.

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Early Follow up	Long Term Follow up	Conclusion
Puri et al 1992 (50)	Retrospective Review Between 1979-1989	11 Type A, EA patients 6M, 5F Mean BW 2040g (1140-2720) Mean gestational age 35wk (28-400 1 Duodenal Atresia in patient with Downs 1 Death All patients had initial gastrostomy Delayed primary anastomosis in all 3 had myotomy At follow up patients/parents interviewed, heights/weights measured, contrast study done and presence of stricture/GER noted	3 Anastomotic leaks 8 Anastomotic strictures All treated with 1-5 dilatations 1 needed stricture resection 4 showed GER in contrast study and managed conservatively	10 survivors Followed up for 18months-11 years 7 excellent result with no feeding or respiratory symptoms 3 Dysphagia Contrast study showed strictures in all 3 patients with dysphagia 3 gross GER (2 with strictures and 1 asymptomatic) Height and weight varied from 3rd-75th centile in 10	Delayed primary anastomosis is feasible in pure EA. Pure Type A EA patients need to be monitored carefully for development of GER which should be treated aggressively.

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Gastric Emptying Study by Scintigraphy	Gastric Manometry	Conclusions
Romeo et al 2000 (51)	Case cohort Study	45 EA Patients operated upon between 1975-1985 22 contacted 11 agreed to be part of study 7F, 4M Median age 17years (13-23) Symptoms: Daily dysphagia in 20% Dyspepsia 4 (40%) (Abdominal distension, fullness, nausea, vomiting, belching, heartburn) GER 2 (Seen in scintigraphy and confirmed by pH Metry) Both had dyspepsia ½ also had dysphagia Both had delayed anastomosis and gastrostomy	Done with solid meal EA 85 minutes (68-125) Control (Historical) 64.5minutes (40-75) p=.001 GES delayed in 4 >90minutes Retention value higher than controls 65% vs 39%, p=.008 2/4 with delayed GES had GER Other 2 were asymptomatic but had abnormal motility in manometry	Basal gastric pressure was positive in all 25-40mbar (normal range) 6 had three fasting phases represented regularly with normal duration of 3rd phase (antral clearing 4-5minutes) 6 had normal peristaltic waves of type I, II and III in both frequency (>3) and amplitude. Peristaltic type III waves in third phase had spikes of normal amplitude (>65 to 70 mbar) 5 had altered duration of third phase (7-11minutes), reduced frequency (<3) and reduced amplitude of type III peristaltic waves (<65-70mbar). Antral hypomotility was caused by increased duration of third fasting phase and a reduced amplitude of type Iii peristaltic waves 1 patient had altered manometry without symptoms or scintigraphic anomalies	EA patients had delayed gastric emptying compared to historical controls, with a pathologically delayed GE in 36%. First study looking at gastric manometry in EA patients. Manometric study of gastric motility showed disturbed peristaltic activity in 45% of EA patients, resulting in antral hypomotility. Motility disorders seen in 20% of EA patients without symptoms Altered gastric motility probably is congenital in origin as unlikely to have been affected during EA repair. Altered gastric motility in EA patients still seen in adulthood, but may not result in symptoms. Gastric manometry can be used to assess dyspepsia in EA patients. Delayed gastric emptying can be an important factor for GER and complicate post-operative course after anti reflux surgery. Hence it should be evaluated in EA patients.

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Anastomotic Leak Recurrent TEF	Stricture	GER	Respiratory Complications Tracheomalacia	Conclusion
Okada et al 1997 (52)	Retrospective Review Between 1957-1995	159 EA patients 3 Groups 1957-1967 : 18 1968-1980: 29 1981-1995: 112 EA Types Type A 8 (5%) Type B (0.6%) Type C 146 (91.8%) Type E 4 (2.5%) Overall survival 27.8% in first period 51.7% in second period 80.4% in third period Waterston Group A 100% Group B 100% Group C 50% Spitz Group A 91.7% Group B 50% Group C 0% Associated anomalies 92 (65.2%) Gastrointestinal Duodenal Atresia 8 Esophageal Stenosis 7 Pyloric Stenosis 3 Biliary Atresia 1	Anastomotic Leakage Second Period 33% Third Period 25.3% Second + Third 26.5% Recurrent TEF Second Period 16.7% Third Period 5.4% Second + Third 7.2%	Second Period 55.6% Third Period 47.9% Second + Third 49.1%	Second Period 25% Third Period 57% Second + Third 52% (53/102) GER diagnosed by ; Contrast study Manometry pH Metry 28/102 (28%) had fundoplication Gastrointestinal symptoms improved post surgery Respiratory symptoms improved in only around 50% Significant increase in weight for height 1 year after fundoplication (n =24, p<.01)	Post-operative pneumonia/atelectasis Second Period 60.9% Third Period 67.1% Second + Third 57% Tracheomalacia 23 cases Second Period 10% Third Period 27.8% Second + Third 25.8% 10 needed Aortopexy	While incidence of early post-operative complications appears to be decreasing due to technical improvements and better perinatal care, long term complications such as tracheomalacia and GER are increasing with the recognition of their pathophysiology

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Feeding Dysphagia	GER	Respiratory	Nutrition Development	Conclusion
Schier et al 2001 (53)	Retrospective Review	128 EA patients Median 14yrs (10-34) **EA Types** Type A 14 (11%) Type B 9 (7%) Type C 93 (73%) Type D 6 (5%) **Anastomosis:** Single operation 99 (77%) 2 Stages 18 (14%) 3 Stages 5 (4%) 4 Stages 1 (1%) 5 Stages 5 (4%) Preoperative elongation by bouginage 19 (15%) Post-operative elongation 8 (8%) Gastrostomy 69 (54%) Esophagostomy 12 (10%) **Gastrostomy complications** 2 ruptures 3 bowel obstructions 1 perforation **Post op complications of EA repair** 4 Recurrent TEF 6 Strictures (resected) 6 Tracheostomy 10 Aortopexy (8%) **Complications of colonic interposition in 8 pts** 3 necrosis 3 strictures 2 colonic insufficiency 1 strabismus **Bouginage** done in 89 (70%) Median 11 (1-350) Median age to which done 24mths (1mth-20yrs) **Complications:** 2 esophageal rupture 2 gastric perforation 1 asphyxia during GA resulting in mental retardation	41 (32%) had no feeding difficulty 68% had some feeding difficulty Pain 24 Regurgitation 21 Vomiting 13 Burping 13 *Duration of symptoms* 1 yr 19 2 yrs 7 3 yrs 4 4 yrs 4 5 yrs 2 6 yrs 2 7 yrs 1 9 yrs 2 No Dysphagia 40 (31%) 69% some dysphagia **Frequency of dysphagia:** Rare 18 pts 1episode 6pts 2 episodes 4pts 3 episodes 4pts 4 episodes 3pts 5 episodes 3pts 10 episodes 2pts 15 episodes 4 pts 20 episodes 1pt 1-2/wk 5pts 304/wk 3pts 1-2/mth 2 pts 2-3/yr 1pt 1/yr 3 pts Daily food impactions 8 Frequent 19	Parents noted GER symptoms in 44 (33%) had Physicians diagnosed GER in 58 (45%) 37 on medications 13 did not name medication 5 antacids 6 H2RA Cisapride 70 (55%) respondents stated they had no GER 20 (16%) had fundoplication 2 had hiatoplasty 14 Type C EA 2 Type A EA 1 Type B EA 3 Type D EA Gap length had no relation to need for fundoplication 7 needed redo of fundoplication **Complications/Outcome of ARS:** 2 bowel obstructions 3 strictures 1 Dumping 4 still had esophagitis 6 still on medications Barrett's 9 (7%) 2 on medications 7 had prior fundoplication	26 (20%) had no respiratory symptoms 80% had > 4 infections/bronchitis/yr Most infections between 3-10 yrs 10 on antibiotics 6 on intermittent steroids 34(26%) had dyspnea with exercise 56 (44%) had noisy breathing 46 (35%) had allergies	94 responses 83 (88%) are of normal height 66 (70%) are of normal weight School 101 (92%) attended regular kindergarden 9 (8%) special needs one 107 (89%) normal school 11% special needs school 64 (52%) above average performance 53 (43%) average 8 (5%) Below average 94 (72%) active in sports107 (82%) sociable 39 (30%) anxious 24 (18%) separation anxiety 24 (18%) withdrawn 47 (36%) need support 17)13%) aggressive	Gastrostomy performed in half the population. They had complication rate of 9% needing reoperation Bouginages had several complications A third of patients had no dysphagia or feeding difficulties Only 25% of fundoplications were successful immediately. Results of medication for GER were inconsistent 80% have respiratory symptoms Increase in respiratory infections between 3-10yrs Only 11% needed special school, which is slightly higher than German national average of 5-9% Support group can provide information database.

		Associated anomalies 86 (67%) Duodenal Atresia 1 Malrotation 1 Meckel 1 Gall Bladder atresia 1 Diaphragmatic hernia 2 Questionnaires sent to families of EA-TEF patients belonging to parent support group where they were >10yrs old 103 questions 128 responded					

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Endoscopy	Conclusion
Schalamon et al 2003 (54)	Observational Retrospective Analysis	74 EA Patients with primary anastomosis follow up period of 0.5-19yrs (Mean 10.3) EA Types Type C EA 72 Type D EA 2 BW Mean 2770g (780-4250) 35 had no associated malformations 39 had associated anamolies18 (24%) had other GI anomalies Anastomotic tension 16 8 myotomy 9 aortopexy	322 endoscopies during in 74 pts **Biopsy graded** into Normal Mild (basal hyperplasia) Moderate (additional inflammatory cells) Severe (erosion) Gastric metaplasia **Histology:** Good: Normal or mild esophagitis Unfavourable: Moderate or severe esophagitis or gastric metaplasia or if had fundoplication (irrespective of histology) 15 normal histology during complete follow up period Mild esophagitis in 30 45 belonged to “Good “ Group 9 had moderate esophagitis 1 Severe esophagitis 13 Gastric Metaplasia 21 had fundoplication 29 had “Unfavourable” findings 33 had no inflammation in initial biopsy 4/33 later had moderate or severe esophagitis or gastric metaplasia In each case change occurred before age 2 years Transition from “Good” to “Unfavourable” outcome seen in 25/29 patients (86%) within 6 months after birth In ¾ remaining patients follow up lost till 5/7/7 years 1 additional patient had delayed endoscopy due to severe associated anomalies If 4 with incomplete follow up were excluded risk of having “Unfavourable” histology after 6 years of repeatedly “Good” biopsies was 0%	40 % of EA patients eventually have significant esophageal mucosal pathology or need fundoplication. Majority of these changes occur by age 3 years. Routine endoscopic follow up is recommended at least till age 3. Endoscopic follow up of all EA patients irrespective of symptoms Patients with repeatedly normal biopsies within 2 years of repair are unlikely to have moderate or severe esophagitis or gastric metaplasia Patients with mild esophagitis should be endoscopically followed up until 6 years of age Approximately half the patients with chronic esophagitis had gastric metaplasia. There is no evidence this reverts to normal. Therefore continuous endoscopic follow up in EA patients with more than minimal esophagitis Endoscopic follow up of children with completely normal biopsies can be discontinued at 3 years In patients with mild esophagitis routine follow up should be expended to 6 years Endoscopic follow up of EA patients can be safely discontinued at some time. This decision is based on histology

GER in EA-TEF

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of Patients
Patient Characteristics
Study Methodology</th><th>Esophageal Morbidity</th><th>Respiratory Morbidity</th><th>Skeletal Abnormalities</th><th>Cancer</th><th>Quality Of Life</th><th>Conclusion</th></tr>
<tr>
<td>Sistonen et al 2011 (55)</td>
<td>Case Control Study</td>
<td>101 EA patients
Controls 287

EA Patients

235 alive EA, 169 responded. First 101 who replied were chosen)

Male 58%
Mean age 36yrs (22-56)
BMI mean 24kg/m2 (21-45)

EA Type
Type A 3 (3%)
Type B 2 (2%)
Type C 91 (91%)
Type D 5 (5%)

Associated anomalies 30%

Anastomotic leak 4%

Recurrent TEF 10%

Stricture requiring resection 4%

Clinical and demographic characteristics of study participants was similar to that of non participants

Methodology:
Symptom questionnaire
Esophageal
Respiratory
Musculoskeletal
QOL (SF 36/GIQLI/RSRQLI)

Age and sex matched controls n=287 filled identical questionnaires</td>
<td>EA Patients
Symptomatic GER 34%
Fundoplication 10%
Dysphagia 85%

Controls
Symptomatic GER 8%
Dysphagia 2%
P<.001 for both

Endoscopy
Hiatal hernia 28%
Barrett’s 11%
Esophagitis 8%
Anastomotic stricture 8%
Diverticulum 3%
Recurrent TEF 1%

Histology
Esophagitis 25%
Epithelial metaplasia 21% (CDX2 +ve)
Gastric 15%
Intestinal 6% (MUC2+ve)
Epithelial metaplasia was associated with esophagitis in 7/21
No dysplasia or carcinoma
Pathology in endoscopy or histology had no correlation with GER symptoms or dysphagia
Patients with metaplasia had more anastomotic complications

<table>
<tr><th>Complication</th><th>All (101) N (%)</th><th>Metaplasia N=21 N (%)</th><th>P value</th></tr>
<tr><td>Early Stricture Resection</td><td>4 (4)</td><td>3 (14)</td><td>0.06</td></tr>
<tr><td>Recurrent TEF</td><td>10 (10)</td><td>6 (29)</td><td>0.02</td></tr>
<tr><td>Late Stricture</td><td>8 (8)</td><td>5 (24)</td><td>0.03</td></tr>
<tr><td>Long gap Requiring myotomy</td><td>5 (5)</td><td>4 (19)</td><td>0.03</td></tr>
</table>
</td>
<td>Significantly more respiratory symptoms, infections, asthma and impaired respiratory QOL compared to controls (p<.002)

EA patients 11% had respiratory symptoms, controls 2%, p<.001
56% and 70% EA patients had pneumonia and bronchitis compared to 20% and 50% of controls, p<.001
16% of EA patients had doctor diagnosed asthma vs 6% in controls, p<.001
Impaired respiratory related QOL in 11% EA patients vs 6% controls, p<.011

Pulmonary function tests showed obstruction 21%, restriction 21%, both 36%
Only 20% had normal lung function
Bronchial hyper responsiveness in 41% and in 15% compatible with asthma
11% had elevated exhaled nitric oxide

Thoracotomy induced rib fusion, surgical complications leading to GER induced epithelial metaplasia were</td>
<td>Vertebral anomalies in 45%
Cervical spine 38%
Risk factor was any additional anomaly
Scoliosis 56%
Risk for scoliosis 13 fold higher than healthy population

Thoracotomy induced rib fusion and associated anomalies were predictors for scoliosis

Clinical course of scoliosis was mild and did not need bracing or surgery

Radial ray anomalies in 25%</td>
<td>No cancer detected despite epithelial metaplasia

3 had cancer in other organs

Overall cancer incidence similar to general population

Statistical risk for esophageal cancer <500 fold that of general population</td>
<td>Significantly decreased general health perceptions (p=.003), increased bodily pain (p=.04). Health related QOL (SF36) was comparable to controls

Mean GIQLI in EA was116+/-22 vs 122+/-22 in controls, p<.005

Mean RSRQLI for EA was 54+/-10 vs 58+/-9 in controls, p<.05

Age (OR 2.6, p<.002) and associated anomalies (OR 8.6, p=.01) predicted poor gastrointestinal QOL

Associated anomalies (OR 7.3, p<.001) and Tracheomalacia (OR 27.4, p<.001) predicted poor respiratory QOL</td>
<td>Long term morbidity in EA adults is significant

Dysphagia, GER and abnormal histology are common

No correlation between symptoms and histology

Surgical complications, increasing age and impaired motility predict epithelial metaplasia

Anastomotic complications impair motility, GER and predispose to metaplasia

No esophageal cancer found but this was a young population and further follow up is needed with long term endoscopic surveillance

Thoracotomy induced rib fusion and GER associated metaplasia were risk factors for restrictive ventilator defect.

Impaired respiratory QOL seen in EA adults

Over half develop scoliosis. Risk is 13 fold higher in EA

Cervical vertebral anomalies and radial ray anomalies reported for first time</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td>Study patients underwent endoscopy and biopsy
Esophageal manometry
Pulmonary function tests

Orthopaedic evaluation with xrays

Incidence of cancer calculated from population based country wide cancer registry</td>
<td>Manometry
Non propagating peristalsis in most
Ineffective distal esophageal pressure in all
All had low distal wave amplitudes, which was lower in those with metaplasia
None of those with metaplasia had propagated peristalsis
Difference between all patients and those with metaplasia was significant, p<.02

Manometric abnormalities significantly more common in those with metaplasia (p<.02)

Anastomotic complications, low distal esophageal pressure, defective peristalsis predicted development of metaplasia
72% of metaplasia patients were male and 76% >30yrs. Metaplasia was associated with increasing age
<table>
<tr><th></th><th>OR (95% CI)</th><th>P value</th></tr>
<tr><td>Early Stricture Requiring Resection</td><td>24 (2.3-260)</td><td>0.008</td></tr>
<tr><td>Recurrent TEF</td><td>24 (2.2-250)</td><td>0.009</td></tr>
<tr><td>>30yrs</td><td>20 (1.3-310)</td><td>0.034</td></tr>
<tr><td>Long gap Requiring Myotomy</td><td>19 (2-180)</td><td>0.011</td></tr>
<tr><td>Late Stricture</td><td>8.6 (1.7-45)</td><td>0.011</td></tr>
<tr><td>Distal wave Amplitude <25mmHg</td><td>2.6 (0.68-10)</td><td>0.002</td></tr>
<tr><td>Non Propagating Peristalsis</td><td>2.2 (0.43-11)</td><td>0.014</td></tr>
</table>
</td>
<td>most significant risk factors for restrictive ventilator defect</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</table>

Table 3 Incidence of gastroesophageal reflux symptoms and histologically proven oesophagitis and Barrett's esophagus in endoscopic long-term follow-up studies

Reference	Age (years) (mean)	GER symptoms	Oesophagitis	Barrett's esophagus
Biller 1987 [32]	22–31 (26)	9/12 (75%)	4/12 (33%)	1/12 (8%)
Krug 1999 [6]	18–26 (22)	13/39 (33%)	9/17 (53%)	2/17 (12%)
Deurloo 2003 [8]	28–45 (34)	15/40 (38%)	19/21 (90%)	1/21 (5%)
Deurloo 2005 [51]	10–26 (17)	23/86 (27%)	30/40 (75%)	0/40 (0%)
Taylor 2007 [12]	20–48 (33)	63/83 (76%)	36/62 (58%)	7/62 (11%)
Sistonen 2010 [13]	22–56 (36)	34/101 (34%)	25/101 (25%)	6/101 (6%)
Total	10–56	157/361 (~43%)	123/253 (~49%)	17/253 (~7%)

Table 4 The six reported cases of esophageal cancer after repair of esophageal atresia

Reference	Age (years) gender	Histology
LaQuaglia 1987 [14]	44 female	Squamous cell carcinoma
Adzick 1989 [15]	20 female	Adenocarcinoma
Deurloo 2001 [16]	38 male	Squamous cell carcinoma
Pultrum 2005 [17]	22 female	Adenocarcinoma
Alfaro 2005 [18]	46 female	Adenocarcinoma
Taylor 2007 [12]	44 not reported	Squamous cell carcinoma

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Fundoplication	Fundoplication Failure	Conclusion
Snyder et al 1997 (56)	Retrospective Review Between 1977-1995 EA-TEF patients who had fundoplication compared to non EA-TEF patients during same period who had fundoplication	!467 Fundoplication in 18 years 1437 (98%) were Thal type 59/1467 (4%) were EA During same time 143 EA patients were repaired 32 (54%) had gastrostomy 59/143 (41%) had fundoplication 58/59 (98%) were Thal Type 1 had Nissen 2 had concomitant pyloroplasty 24 F, 35M Mean age at fundoplication 21months (10days-13yrs) Long gap (>2cm) 12 Myotomy 8 (14%) Neurological impairment seen in 6/59 (10%)	59 Fundoplications **Indications:** **Gastrointestinal** Vomiting 50 Failure to thrive 39 **Respiratory** Recurrent pneumonia 27 Chronic cough 12 ALTE 13 Choking 20 Asthma 2 Croup 2 **Inflammatory** Stricture 38 Anemia 3 Irritability 3 Bleeding 1	Overall failure rate (defined strictly as need for re operation) for the 1408 non EA patients was 4.2% Failure rate in EA-TEF was 9 (15%) This was significantly higher than the failure rate in non EA pts , p<.001 2 had third fundoplication All 9 failures were after Thal 6/9 had repeat Thal 3/9 had Nissen Wrap disruption seen in 4/9 Slippage of intact wrap in 2/9 Intact fundoplication in 3/9 at time of redo Re redo 1 Nissen converted to Thal 1 Thal re operated on as Thal Presence of gastrostomy, long gap or prior myotomy differed significantly in children with fundoplication failure compared to those with successful fundoplication Respiratory symptoms (recurrent pneumonia) occurred in all patients who needed redo 2/9 failures were neurologically impaired	Mean incidence of GER requiring fundoplication was 41% which was higher than that reported (13%) in previous series (Table 1) This could be because authors treated GER aggressively and 64% stricture rate attests to presence of significant GER in this series Failure rate of partial fundoplication (15%) was significantly higher than that (4.2%) in non EA-TEF patients. Short esophagus, esophageal dysmotility might have contributed to this. However Thal fundoplication was still twice as successful as the results in literature for Nissen fundoplication (Table 2) 33% failure rate in neurologically impaired EA-TEF children. If they were excluded there was still a failure rate of 7/53 (13%) Partial wrap (Thal)fundoplication appears to clinically offer better results than complete wrap (Nissen) in EA-TEF patients

Table 1. Percentage of Patients Requiring Fundoplication After EA/TAF Repair

Study	Year	EA/TEF (n)	FUNDO, n (%)
Montgomery and Frenckner[12]	1993	110	9 (8)
Wheatley et al[1]	1993	80	21 (26)
Touloukian[4]	1992	68	5 (7)
Black et al[5]	1991	97	16 (16)
Myers et al[6]	1990	498	33 (7)
McKinnon and Kosloske[7]	1990	61	8 (13)
Curci and Dibbons[3]	1988	31	14 (45)
Sillen et al[9]	1988	103	6 (6)
Manning et al[8]	1986	58	17 (29)
Mercier et al[10]	1984	73	14 (19)
Gauthier et al[11]	1980	113	15 (13)
Parker et al[16]	1979	17	6 (35)
Current study	1996	143	59 (41)
Totals*		1309	164 (13)

NOTE. Significant variation exists between different institutions regarding the need for fundoplication in patients who underwent prior EA/TEF repair.

*Authors' data not included.

Table 2. Failure of Nissen Fundoplication in Patients Who Had Prior EA/TEF Repair

Study	Year	EA/TEF (n)	FUNDO, n (%)	Failures, n (%)
Wheatley et al[1]	1993	80	21 (26)	7 (33)
Lindahl et al[2]	1989	48	13 (27)	5 (38)
Curci and Dibbins[3]	1988	31	14 (45)	5 (36)
Fonkalsrud[13]	1979	14	9 (64)	0 (0)
Current study	1996	143	59 (41)	9 (15)
Totals*		173	57 (33)	17 (30)

NOTE. Nearly one third of patients had a poor outcome after complete wrap for GER associated with EA/TEF.

*Authors' data not included.

GER in EA-TEF

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of Patients
Patient Characteristics</th><th>Post-Operative Complications</th><th>Gastrointestinal Morbidity</th><th>Respiratory Morbidity</th><th>Survival</th><th>Conclusion</th></tr>
<tr>
<td>Seo et al
2010 (57)</td>
<td>Retrospective Review
Between 1990-2007</td>
<td>97 EA patients
Follow up 2years

Maternal characteristics:
Mean Age 30+/-3.8yrs
Primigravida 28/91 (31%)
Polyhydramnios 27/91 (30%)
Prenatal diagnosis 6/50 (12%)
Pregnancy associated HT 19/71 (26%)

EA patients
Gestational age 37+/-3 (26-43)
Prematurity 31/97 (32%)
BW 2.5+/-0.7Kg
Male: Female 60:40
Apgar
1min ^+/-2
5min 8+/-2
Vaginal:LSCS 47:52
Average hospital stay 41+/-47
Twinning 5%
(both fraternal twins had EA-TEF)
51% had at least 1 congenital anomaly
41% VACTERL
Gastrointestinal 24%
Duodenal atresia
Pyloric stenosis
Malrotation
Biliary atresia

EA Types
Type A 2 (2%)
Type B 1 (1%)
Type C 71 (91%)
Type D 1 (1%)
Type E 3 (4%)

Surgery
On average day 4 in 87 neonates
Primary repair 72 (88%)
Average gap length 2cm(1.4-3)
8 had gastrostomy or duodenostomy
2 esophageal replacement
Ventilator 9.6days (1-106)</td>
<td>Contrast study done on an average of 25 days

Anastomotic leaks 9 (12%)</td>
<td>72 were followed up 2yrs

GER 29 (38%)

Dysphagia 65%

Anastomotic stricture 47 (64%)
26 showed stricture on average 3months after surgery
Balloon dilatation on average 1.3times/patient
Recurrent fistula 2

At 1 yr
Weight <10th Centile 48%
Below 3rd Centile 19%

At 2yrs
Weight <10th Centile in 45%

About a third of patients with “Gap” >2cms had anastomotic leak, recurrent TEF, GER and stricture as post-operative complications

7 patients with ultra-long gap (>3cms), 4 died, 2 had failure to thrive and only 1 had normal growth for age</td>
<td>72 were followed up 2yrs

Laryngomalacia 2%
Cricopharyngeal incoordination 4%
Recurrent pneumonia 4%
Tracheostomy 5%</td>
<td>Mortality

1990-1999 39%
2000-2007 23%
Overall mortality 20%

Cause of death:
Sepsis
Respiratory failure
Endocarditis
CCF
GIT hemorrhage
Liver cirrhosis
Gastric perforation

Of 40 with VACTERL 30% died
Cardiac + VACTERL 16%

Survival in full term 87%
Survival in premature infants 62%

Univariate analysis of factors affecting mortality:

<table>
<tr><th>Variables</th><th>OR</th><th>P</th></tr>
<tr><td>Gestational Age</td><td>0.97</td><td>.006</td></tr>
<tr><td>BW</td><td>0.99</td><td>.020</td></tr>
<tr><td>Apgar 1min</td><td>0.70</td><td>.014.010</td></tr>
<tr><td>Apgar 5min</td><td>0.60</td><td>.030</td></tr>
<tr><td>Ventilator days</td><td>7.30</td><td>.012</td></tr>
</table>

P value was not significant for cardiac anomalies, EA type, day of surgery and days in hospital

Effect of cardiac anomalies and BW on survival
No CHD+BW>1500g 78%
CHD or BW>1500g 67%
CHD+BW<1500g 0%</td>
<td>Gastrointestinal complications were more common than respiratory in this study

Overall mortality rate (20%) and morbidity rate (67%) are due to associated anomalies and gastrointestinal and respiratory complications

Long term follow up into childhood and adulthood is needed</td>
</tr>
</table>

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Fundoplication	Conclusion
Wheatley et al 1993 (58)	Retrospective Review Between 1974-1988	62 EA-TEF studied for average follow up of 62 months 80 EA patients born 8 not treated or died 5 had esophageal replacement 67 repaired by single or staged procedure Gastrostomy in 59/67 (88%) 5 lost to follow up	GER diagnosed on history and barium swallow in 34 (55%) **Medical treatment:** Thickened upright feeds Metoclopramide Medical therapy successful in 7 (21%) Failed in 27 (79%) 21/27 had Nissen fundoplication with Stamm Gastrostomy and posterior fixation of the wrap to the diaphragmatic hiatus 5 still on medications at parents request. They still have problems with aspiration and dysphagia 1 died intraoperative at time of fundoplication **21 Fundoplication** 8 (38%) excellent reflux control with no postoperative dysphagia 7 (33%) developed recurrent reflux Significantly higher than the 10% recurrent reflux seen in the non EA patients who had fundoplication at the same hospital in that period GER eliminated in 18/21 following initial or redo fundoplication but: 6 had prolonged dysphagia and were gastrostomy dependent for at least 6 months 3 still gastrostomy dependent years after the surgery Fundoplication outcome shown in Figure 1	Medical management of GER failed in 80% in this study Of total group 15 (71%) had excellent long term result with regard to reflux control and absence of dysphagia long term but there was significant morbidity and mortality Fundoplication breakdown is probably higher in this series because of longer follow up and due to tension on fundoplication from shortened esophagus Post-operative dysphagia was common, occurring in 50% of cases. This could be due to dyskinetic esophagus being unable to overcome the resistance of the valve mechanism in Nissen, the children not having been able to swallow normally preop due to severe GER, developmental delay and coexistent illness. 15/18 with successful fundoplication eventually were able to feed by mouth exclusively Management of GER remains problem in EA, prevention might be best option by limiting routine gastrostomy and limited mobilization of distal esophagus Medical treatment is of limited value although in this study only thickened feeds and metoclopramide were used Authors no longer do Nissen but do 180 anterior fundoplication. Long term follow up needed to see whether incidence of dysphagia and fundoplication failure is reduced with this operation.

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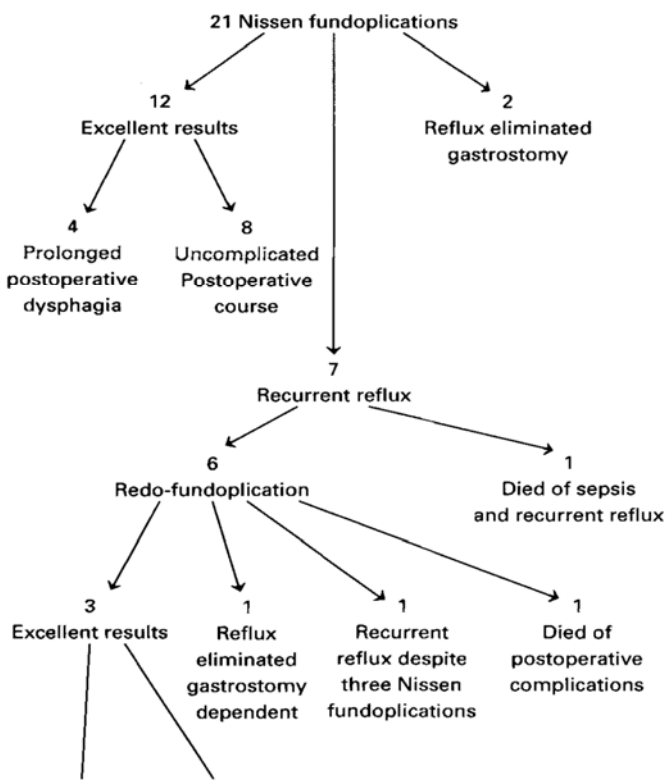
21 Nissen fundoplications
12
Excellent results
2
Reflux eliminated gastrostomy
4
Prolonged postoperative dysphagia
8
Uncomplicated Postoperative course
7
Recurrent reflux
6
Redo-fundoplication
1
Died of sepsis and recurrent reflux
3
Excellent results
1
Reflux eliminated gastrostomy dependent
1
Recurrent reflux despite three Nissen fundoplications
1
Died of postoperative complications

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Gastric Emptying Study	Conclusion
Montgomery et al 1998 (59)	Case Control Study	**10 EA Patients** Primary anastomosis No undue tension No myotomy No neurological impairment or severe associated malformations 6M Median age 7.5Years (5-10) **Symptoms in EA patients**: 5 had mild dysphagia 6 had GER symptoms 4 had asthma 4 had abdominal symptoms (2 distension, 2 pain) 3/6with GER symptoms had pH Metry 2 showed reflux **11 healthy controls** Median age 7 years (5-11) No symptoms of reflux, dysphagia or abdominal complaints	Solid gastric emptying study Meal consisted of pancakes (milk substitute used to overcome allergic to dairy) with fixed energy composition labeled with Tc-99m. Pancake cut into standardized pieces. Eaten within 10min. Fractional meal retention values plotted as a function of time. In vitro test carried out to determine stability of the Tc-99 labeling of the solid phase of the meal where pancake was mixed with gastric juice and incubated and shaken at 37o for 2 hours. Results showed firm binding of the radioactive marker to the solid phase of the meal with 97% (96-99) remaining after 2 hours in the gastric juice **Results** **Table 2 shows results GES in EA patients and controls** T50 values, lag phase, corrected T50 values were significantly longer in the patient group than in the control group. Patient group showed significantly higher retention values at 60 and 90 minutes and slower emptying rates than control group. Retention values at 120 minutes were very low or close to 0 in many of the healthy control (? Because of the low amount of isotope used). Hence the 120 minute values could not be used in analysis because of the difficulty in estimating correct values 3 of the patients had retention at 60 and 90 minutes outside 2SD of the controls	Scintigraphy is an easy and reliable noninvasive method for gastric emptying studies Gastric emptying has not been studied in healthy children before. For ethical reasons the activity of the isotope was kept very low (0.5-1MBq) To reduce error volume/energy content of meal was adjusted to body weight and pancake was cut into standardized pieces. The values of healthy children for gastric emptying correspond to those from healthy adults in previous studies AS EA patients chew food well size of the food particles could not explain the longer lag phase that they had compared to controls DEA children showed slower gastric emptying than healthy control children. All parameters (T50, lag phase and corrected T50) were significantly longer in the patient group. The retention values at 60 and 90 minutes were significantly higher and the emptying rates (percent per hour) were lower. However there was considerable overlap in individual data. 2 patients with GER showed long lag phase and slow gastric emptying However there was no difference in gastric emptying rate between patients with symptoms (reflux or abdominal) and patients without symptoms. Delayed gastric emptying might contribute to reflux symptoms in some patients with repaired EA. Delayed gastric emptying could be congenital or caused by operative trauma or post-operative complications (anastomotic leak or infection).

Table 2. Results of Scintigraphic Gastric Emptying of Solids in 11 Healthy Children and 10 Patients With Repaired Esophageal Atresia

Variable	Control Group (n = 11)	Patient Group (n = 10)
T50 (min)	78 (62-110)	100 (78-173)
Lag phase (min)	21 (9-47)	34 (20-68)
Corr. T50 (T50-lag)	53 (44-76)	62 (48-105)
Emptying rate (%/hour)	46 (31-55)	40 (23-50)
Retention 60 min (%)	63 (47-82)	75 (63-97)
Retention 90 min (%)	40 (26-66)	56 (42-83)

NOTE. Control group patients were age 5 to 11 years; median, 7 years. Patient group was age 5 to 10 years; median, 7.5 years. Values are expressed as medians and ranges and are statistically significant.

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Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Gastrointestinal: Stricture Dysphagia GER Gastrostomy Fundoplication	Tracheomalacia "Cyanotic Spells" Aortopexy	Respiratory	Sub Groups Long Gap Foker	Conclusion
Shah et al 2014 (60)	Retrospective Review Between 1999-2010	110 EA patients 10 excluded due to incomplete data Male 45% Mean Gestation 36.4 wk(SD 3.2) Mean BW 2620g (702.1) 6 Twins Mean age of patient at time of study 6yrs (3.5) Mean age of patient at time of repair 1 day (1.09) 14% VACTERL 5% CHARGE Follow Up 64 <1yr 18 (1-5)yrs 18 >15yrs at time of study No deaths EA Types: Type A 7% Type B 1% Type C 91% Type D 0 Type E 1% Surgical complications: Anastomotic Tension 2% Anastomotic Leak 3% Pneumothorax 12%	**Dysphagia** 11/100 (11%) Median age 22mths (12-26) 4/11 (36.4%) required endoscopic removal of food bolus 9/11 (81.8%) had GER 3/11 (27.3%) had Eosinophilic esophagitis (EE) **Strictures** **Early Stricture (<1yr)** 31/100 (31%) Long gap EA was predictor for early strictures (OR 16.32, CI 1.8-142.5) on univariate analysis **Dilatations:** 69% had no dilatation 16% had 1 dilatation 7% had 2 dilatation 3% had 3 dilatation 5% had 4 or more dilatation **Late Stricture (>1yr)** 15/100 (15%) 6/15 had early strictures Long gap EA was a predictor for late stricture (OR 5.5, CI 1.6-19.1) GERD was predictor for late stricture (OR 9.9 CI 1.9-50.4) on univariate analysis **Dilatations:** 56% had no dilatation 8% had 1 dilatation 5% had 2 dilatation 1% had 3 dilatation 1% had 4 or more dilatations	All had Laryngobronchoscopy (LB) at birth 31 had subsequent LB 22.6% had mild tracheomalacia 25.8% had moderate 32.2% had severe tracheomalacia 19.4% was normal 7 had cyanotic spells All had severe tracheomalacia on LB Severe tracheomalacia was predictor for cyanotic spells (OR 180 CI 16.1-2004) and aortopexy (OR 549 CI 24-2.5) **Aortopexy** 2/7 had initial aortopexy with improvement 5/7 had initial fundoplication with persistent symptoms and needed subsequent aortopexy On univariate analysis severe tracheomalacia (OR 549 CI 24-12), GERD (OR 6.4 CI 1.3-31.5) and fundoplication (OR 16.8 CI 2.9-96.99) were predictors for aortopexy. On multivariate analysis severe tracheomalcia and fundoplication were predictors for aortopexy (p=.001)	19 cough/wheeze 23 chest infections Patients with early stricture were significantly more likely to develop recurrent chest infections (OR 3.33, CI 1.2-8.7) Spirometry 8 Median age 8yrs (6-10) 62.% were abnormal 14 had reactive airway disease 8 had bronchodilator challenge median age 6yrs (6-9) 5/8 were abnormal	**Long Gap (LG)** 7 had LG EA Median time for anastomosis 57 days (7-107) Native esophagus 100% All had gastrostomy 1 fundoplication 4 had gastrostomy at 1yr 2 had gastrostomy at 2 yrs Compared to non long gap LG EA were more likely to have gastrostomy at 1yr (OR 14.1 CI 2.6-74.7) No difference at age 2yrs 3/7 (42.9%) developed EE Both early (OR 16.3 CI 1.8-142.5) and late strictures (p=.007) were more likely in LG EA **Foker** 5 patients Median gestational age 35wks Median BW 2560g 3/7 had associated anomalies Median time to anastomosis 57days (15-107) Average of 9 dilatations/patient for strictures These patients had more dilations/patient when they were <1yr vs 1/patient in non Foker group and 3/patient in LG EA All had gastrostomy at birth At review all had gastrostomy closed and were eating normally 33.3% were on PPI for GERD No fundoplications 2/5 (40%) developed EE	Predictive factors were identified for occurrence of early and late complications in EA-TEF patients Long Gap EA was a predictive factor for early and late strictures 4/9 with denovo late strictures (no early stricture in the patient) had EE. Important to exclude EE in all late strictures with endoscopy and biopsy. Not all late strictures are due to GERD Majority of patients with dysphagia had GERD, but 27.3% also had EE. All EE patients had dysphagia and third had strictures No correlation between GERD symptoms and histology No Barrett's diagnosed in this study Gastrostomy was a significant predictor for having a fundoplication. This could be because severe GERD with vomiting often necessitates a gastrostomy, gastrostomy can worsen GERD, long gap EA often require gastrostomy and LG can worsen GERD Important to exclude strictures in patients with chest infections as early strictures were a

			On multivariate analysis only long gap was predictor for early and ate stricture (p=.007) Late stricture was not a predictor for chest infections **GERD** 20/100 (20%) had symptoms of GER Median age 4.5yrs (1-10) **Investigations:** **pH Metry** 4 1 was abnormal **pH-Impedance** 12 on PPI 2 were abnormal (elevate RI or abnormal SI or SAP) **Endoscopy** 38 had 1 21 had 2 11 had 3 **First gastroscopy** 28.9% mild esophagitis 5.3% moderate esophagitis 2.6% severe esophagitis **Second Gastroscopy** 42.9% mild esophagitis 4.8% moderate esophagitis **Third gastroscopy** 18.2% mild esophagitis 9.1% moderate esophagitis No correlation between reflux symptoms and histology **Treatment of GER** **Medication** 39% were on medications (PPI or H2RA) 38.5% had persistent symptoms on medication				predictor for chest infections 71.4% of patients with cyanotic spells who had fundoplication had persistent symptoms and needed subsequent aortopexy. Hence important to investigate cause of dying spell with LB, endoscopy, pH impedance before deciding on aortopexy or fundoplication or both

			GERD was a predictor for fundoplication, p=.007 GERD was a predictor for aortopexy (OR 6.4 CI 1.3-31.5) **Fundoplication** 17/100 (17%) had fundoplication Median age 12mths (3-36) Prior to fundoplication 47.1% had Barium study- all normal 1 had pH Metry which was abnormal 35.3% had endoscopy in which 3/6 showed mild, 2/6 showed moderate and 1/6 showed severe esophagitis On univariate analysis severe tracheomalacia (OR 8.2 CI 1.9-35), gastrostomy (OR8.2 CI 2.5-26.1) and cyanotic spells (OR 16.8 CI 2.9-96.9) were predictors for undergoing a fundoplication On multivariate analysis only a gastrostomy was a predictor for fundoplication, p=.00 **Gastrostomy** 19% had gastrostomy median time of insertion 1 day (1 (0-120) 6/19 (31.6%) were long gap EA 9/13 had gastrostomy at time of fundoplication 4/13 had it for feeding difficulties/vomiting due to GERD At 1 yr 12/100 had gastrostomy At2yr 10/100 had gastrostomy On univariate analysis both long gap EA (OR 36.9 CI 4.1-322.3) and GERD (OR 5.7 CI 1.9-17.2) were predictors for gastrostomy.				

			This was true on multivariate analysis too, Long gap p =.001, GERD, p=.002 Gastrostomy was a predictor for GERD, p=.002 Gastrostomy was a predictor for subsequent fundoplication, p<.001 **Eosinophilic esophagitis (EE)** 6 patients All on PPI at diagnosis Budesonide slurry 6/6 Food exclusion 3/6 50% were long gap EA two thirds of LG EA + EE had EE strictures 4/6 developed late strictures EE was not a predictor for late stricture				

Author/Year	Study Type	Number of Patients Patient Characteristics	Esophageal Symptoms	Respiratory Symptoms	Endoscopy	Conclusion
Taylor et al 2007 (61)	Case cohort descriptive study	132 EA adults attended clinic between 2000-2003 Mean age 33 (20-48) Male 78 (59%) Associated anomaly 21 (16%)	GER symptoms 83 (63%) Heartburn/acid regurgitation Mild: < fortnightly 45 (34%) Moderate< >fortnightly 13 (105) Severe: 3/week 25 (19%) On medications 35 (27%) PPI 8 (6%) H2RA 10 (8%) Antacids 17 (13%) 8/25 with severe symptoms were on medications Prior Fundoplication 14 (11%) Dysphagia 68 (52%) 3/wk 41 (31%) Dietary modification 47 (36%) Additional fluid 41 (31%) Soft diet 6 (5%)	44 (33%) had respiratory symptoms in last 1 yr Asthma 29 (22%) Bronchitis 6 (5%) Pneumonia 4 (3%) Cough 5 (4%) 75 (57%) had respiratory symptoms at some stage in their lives Asthma 34 (26%) Bronchitis /cough 32 (24%) Pneumonia 19 (14%)	Endoscopy offered to all those with GER symptoms Results of previous endoscopy in last 5 years looked up Esophagitis graded as per Hetzel Dent Histological Barrett's confirmed only if Intestinal Metaplasia (IM) **Histology** Esophagitis seen in 36 (58%) Mild (Grade 1) 5 (8%) Moderate (Grade 2) 25 (40%) Severe (Grade 3-4) 6 (10%) Barrett's endoscopically in 16 IM confirmed in 7 (11%) Long segment >3cm 4 Short segment 3 Low grade dysplasia 3 (all long segment) Only 2 of 7 with severe GER symptoms was on treatment 1 with moderate symptoms was on treatment Both with mild symptoms were not on treatment Of 7 with severe symptoms 5 Grade 3 1 Grade 2 1 Grade 4 3 Barrett's Of 7 Barrett's 3 had severe GER symptoms 1 had moderate symptoms 2 had mild symptoms 1 had no symptoms 2 were on antacids **Endoscopic Strictures** Seen in 26 (42%) 25 at anastomotic site Distal strictures 3 2 both anastomotic	Attendance at a multidisciplinary EA-TEF clinic for adults resulted in reflux medication started in 22 patients (18 PPI/4 H2RA) Barrett's surveillance started in 7 9 had dilatation of strictures Management changes in 30/132 (23%) Patients with severe GER symptoms had higher incidence of severe esophagitis and Barrett's Men aged 35 years and older were at risk for serous esophageal pathology especially if they had severe GER symptoms Not all Barrett's patients had symptoms. Hence surveillance needed for these patients. As SCC developed at anastomotic site, any patient with increasing dysphagia needs to have endoscopy and biopsy Surprisingly only 2/6 patients with moderate or severe strictures had esophagitis Not all who had bouginage of strictures improved, ? because balloon dilatation is superior or because dysphagia was because of dysmotility **Recommendations:** All EA-TEF patients should be assessed between 15-25 years Endoscopy should be offered to all with GER symptoms especially male patients Esophagitis and Barrett's should be treated aggressively with medications or fundoplication

					6 (10%) had moderate stricture 1 severe stricture 19 mild stricture 6/7 with moderate stricture was at anastomotic site 2/6 had esophagitis 9 had bougie dilatations 3/5 had improvement in dysphagia **Esophageal malignancy** No adenocarcinoma seen 1 squamous cell carcinoma at anastomotic site Risk factors for severe reflux esophagitis and Barrett's 1. Males 35 years and older were at a higher risk Of 25 of these men who had endoscopy 6 (24%) had severe esophageal disease 2. Those with severe reflux symptoms 6/21 patients with severe symptoms had severe esophageal disease Of 15 patients without symptoms who had endoscopy only 1 had Barrett's without dysplasia	Worsening dysphagia should be investigated with endoscopy with attention to anastomotic site Optimal method of dilatation needs to be defined Additional data needed to determine whether asymptomatic patients need routine endoscopic surveillance

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Author/Year	Study Type	Number of Patients Patient Characteristics	pH-Impedance	Impedance Manometry	Gastric Emptying	Conclusion
Van Wijk et al 2013 (62)	Prospective case cohort study 2006-2008	10 consecutive infants with EA 10 randomly selected EA adults **Infants** Type C EA 100% Age 0.67yrs (0.23-3.42) 5M BW 2900g (1340-3940) Gestational age 38.5wks (31-40) PPI use 100% **Adults** Type C EA 100% Age 24.5yrs (18.1-31.3) 6M BW 2470g (1480-3880) Gestational age 39wks (30-41) PPI use 40% No patient had chronic respiratory disease or RTI at time of study	3529minutes of tracings 306RBM 181 (59.2%) were liquid 77 (25.2%) were mixed 48 (15.7%) were pure gas 97 (31.7%) was acidic 192 (62.7%) was weakly acidic 17 (5.6%) was weakly alkaline **Infants** 101 liquid 37 mixed 27 pure gas 34 acidic 114 weakly acidic 17 weakly alkaline 42 proximal GER 123 non proximal GER **Adults** 80 liquid 40 mixed 21 pure gas 63 acid 78 weakly acid 15 proximal GER 126 non proximal GER The median number of GER episodes per patient was not significantly different between infants 14 (9-33) and adults 9.5 (4-44), p=.23	**Manometry during reflux detection** 228 TLESRs were identified 31 were not accompanied by GER episode seen on MII Of 306 GER events 197 (64.4%) occurred during TLESR 28 (9.2%) were caused by swallow related LES relaxations (SLESR) 27 (8.8%) were due to straining 13 (4.2%) were due to multiple swallow related LES relaxations (MLESR) 7 (2.3%) due to low LES baseline 34 (11.1%) no mechanism could be identified **Infants** TLESR 66% SLESR 10% MLESR 2% Straining 12% Unidentified 10% **Type of GER associated with TLESR in infants** 55% Liquid 24% Mixed 21% Gas **Adults** TLESR 62% SLESR 9% MLESR 6% Low LES baseline 5% Straining 6% Unidentified 12% **Type of GER associated with TLESR in adults** Liquid 49% Mixed 35% Gas 16% There was a statistically significant difference between distribution of GER events in infants and adults	C13 Octanoate breath test was used. Infants were given liquid meal and adults had a solid meal T1/2 GES was compared to age, meal and sex appropriate normal values GES data available for 7 infants and 9 adults Infants T1/2 107.8min (54-173.7) Delayed (>75th centile) 5 (71.4%) Delayed >90th centile 4 (57.1%) Adults T1/2 98min (45.4-120.7) Delayed (>75th centile) 5 (55.5%) Delayed >90th centile 2 (22.2%) No statistically significant difference between children and adults No association was found between GET1/2 and esophageal motility, p=.32 or between GET1/2 and bolus clearance, p=.23	First study combining MII, manometry and gastric emptying data to evaluate mechanisms underlying GER events and gastroesophageal function in EA Type C TLESR is the main mechanism underlying GER episodes in EA Type C patients both shortly after primary anastomosis and in adulthood No difference found in total number of GER episodes between infants and adults but adults had more acid GER events and less GER episodes reached proximal esophagus. This could be because in the supine position of the infants the acid pocket is less likely to have an effect, in addition to the relative larger meal volume in infants and increased acid secretion in adults Esophageal dysmotility seen in nearly all children with EA. The most common abnormality was lack of propagation of peristaltic wave into distal esophagus Abnormal esophageal motility resulted in abnormal clearance which can potentially increase risk for esophagitis and carcinoma in these patients Majority of infants and adults had delayed gastric emptying No correlation seen between gastric emptying and severity of esophageal motor abnormalities or GER episodes Abnormalities in gastrointestinal function seen in this study underline the importance of monitoring in these patients from childhood to adulthood

				Of all 306 MII detected GER episodes 34 (11%) were followed by primary peristalsis 71 (23.2%) by secondary peristalsis In 201 (65.7%) there was no clearing mechanism following GER episode **Motility Patterns** A median of 17 (5-22) boluses/patient could be analysed Total 324 64 boluses were excluded as they were infused in proximal esophagus rather than swallowed 260 analyzable swallows 55 (21.2%) had normal peristalsis Normal peristalsis seen in 4 infants and 2 adults Of these 6 1 adult had normal motility in 80% of swallows 5/6 >50% of swallows had abnormal motility **No normal peristalsis seen in 14 (70%) patients** In 120/205 swallows that did not fulfill criteria for normal peristaltic wave, normal peristalsis was seen in proximal esophagus but did not propagate distally (58.5% of swallows with abnormal peristalsis and 46.2% of all analyzable bolus swallows Other peristaltic abnormalities: Focal failure in peristalsis 41 (15.8%) Generalised failure 27 (10.4% Synchronous contractions 17 (6.5%) **Mean LES pressure preceding a swallow was 13.1+/- 10.1mmHg** **LES relaxation was complete in 271 (83.6%) swallows**		

				In normally propagated contractions: 28 (50.9%) were normotensive 21 (38.2%) hypotensive 6 (10.9%) hypertensive Data was similar in infants and adults **Motility and bolus clearance In 264 boluses** Median 15 (3-20)/patient were both impedance and manometry tracings were analyzable MII showed complete bolus clearance in 108/263 (40.9%) of swallows This figure did not change significantly when infused boluses were not included (79/200, 39.5%, p=.83) **Clearance results and TBTT are shown in Table 2** No significant differences between liquid and viscous boluses (p=.15) Upright and supine position (p=0.54) Infants and adults (p=.85) Normal motility caused significantly more normal clearance (47/55 (85.5%) boluses) compared to abnormal motility (61/205 (29.7%) boluses), p<.0001		

Table 2 Bolus clearance as detected by multichannel intraluminal impedance.

	Infants				Adults			
	Liquid		Viscous		Liquid		Viscous	
	Supine	Upright	Supine	Upright	Supine	Upright	Supine	Upright
Normal clearance	13 (46%)	11 (55%)	9 (33%)	12 (38%)	16 (41%)	19 (45)%	11 (33%)	17 (40%)
TBTT	14 (6–141)	13 (3–86)	18 (12–224)	15 (4–111)	14 (5–64)	13 (5–162)	16 (9–48.4)	13 (4–121)

Normal clearance is shown as number of patients (%). Total bolus transit time (TBTT) is shown as median (range). Note that in the latter parameter boluses infused in the proximal esophagus are not included in the analysis.

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Author/Year	Study Type	Number of Patients Patient Characteristics	Symptoms	Physical Examination	pH Metry	Endoscopy	Esophageal Manometry	Lung Function Testing	Tracheobronchoscopy	Conclusion
Somppi et al 1998 (63)	Case cohort study	60 EA patients repaired between 1963-1993 6 had tracheomalacia 3 had subtotal thymectomy and aorrtopexy at 1-3yrs 5 had fundoplication from 1-6yrs 1 had a redo 6 (10%) died 1 from ventricular rupture after fundoplication	Questionnaire on respiratory and GI symptoms used 43 completed it In past year: 9 (29.3%) had respiratory infections 14 (32.3%) got antibiotics 12 had recurrent dyspnea 5 had asthma 15 (34.9%) had dysphagia 11/15 <7yrs old GER 8 (18%) 16 (37.2%) night coughs 14 (32.3%) had impaired QOL Average number of complaints < with age 4.7 <10yrs 10-20yrs 2.3 >20yrs 2	42 patients Mean age 12.6yrs (3.5-30) Mean height for age -0.34 (0.96) Mean weight for height 8.3% (23.8) 2 (4.9%) height was below 2SD (-2.1-2.4SD) Weight for height was below -10% in 7 (16.5%) >10% in 12 (28.6%) Range -23-77% All normotensive Scoliosis 9 Limb anomalies 7 Medication 4 for asthma 4 for GER	41 cases No GER 32 (78%) 3 (7%) had distal GER 6 (15%) had proximal GER 2 with GER had no symptoms 6 with symptoms had no GER in pH Metry	41 cases 6/41 had colon interposition These 6 had normal mucosa **Macroscopically** Normal in 31/35 Mild inflammation 1 Severe inflammation 1 Barrett's 2 Cardiac insufficiency 4 (10%) Mild gastric body inflammation 5 (12%) Ectopic pancreas 2 (5%) Nodular antral gastritis 1 (2%) Biliary reflux 7 (17%) **Histology** Normal 15 (43%) Mild inflammation 13 (31%) Severe inflammation 7 (20%) Gastric metaplasia 2 (6%) In all colon esophageal biopsies were normal 8 (21%) had H Pylori in biopsy and urease test Dependence of esophageal inflammation on pH values was significant, p=.002	Manometry in 31 cases (76%) Esophageal transit time test in 37 (90%) Abnormal peristalsis 75% Abnormal LES function 7% Abnormal esophageal transit time 12% In colon esophagus Abnormal peristalsis 100% Abnormal LES function 100% Abnormal esophageal transit time 50%	24 cases Normal 8 (33%) Slightly <predicted 12 (50%) Moderately abnormal 4 (17%) No severely abnormal results Reversibility with bronchodilators 2	Tracheal lumen was normal 23 (66%) Slightly narrowed 8 (23%) Moderately narrowed 4 (11%) In colon esophagus the results were similar for tracheal lumen **Tracheal inflammatory changes on biopsy and endoscopy are shown in Table 1** Esophageal ectopy was seen in 2 (5%) Dependence of tracheal inflammatory changes on esophageal pH values and motility was significant, $p=2.76 \times 10^{-6}$ and p=.002 respectively	Severity of GER, esophageal peristaltic abnormality, tracheal inflammation and impairment of lung function appears to alleviate with age Esophageal inflammatory changes do not improve with age Esophageal transit time increased with age Dysphagia, food impaction and prolonged meal times occur in >50% of cases during first 5 years after repair. Patients with problems >7yrs were those with colon interposition Growth retardation was not seen and patients were more frequently overweight Signs of lower respiratory tract disease seen in 60% Signs of tracheomalacia dominate early on while lower airway obstruction occurs later Rate of GER on pH Metry was low

										Discrepancy between subjective GER symptoms and pH Metry results Fundoplication rate (9%) was low but there was 1 mortality Abnormal esophageal peristalsis seen in majority but LES pressure was normal in 71% of cases. These abnormalities did not affect transit time which was normal. Transit time was prolonged in 50% of cases with colon interposition. Surprisingly patient did not complain of prolonged meal times Lower rate of esophagitis compared to other studies could be due to older age No dependence seen between esophageal inflammation and dysmotility High positive rate of H Pylori seen. Whether EA predisposes to H Pylori needs to be investigated First study to look at histopathologic examination of trachea. High rate of severe inflammation seen in trachea which

										cannot be explained by infections. These patients often had night cough, 4 were asthmatic. GER on pH Metry and esophageal function abnormalities correlated with tracheal inflammatory changes. Thus delayed acid clearance and GER might induce tracheal inflammation and result in nocturnal cough. Further outcome studies needed to look at effect of GER treatment on respiratory symptoms and tracheal inflammation Gastric metaplasia and high rates of esophageal, gastric and tracheal inflammation demonstrate the need for long term follow up in EA patients

Table 1. Incidence of Tracheal Inflammation in Primary Anastomosis and in Colon Esophagus Patients

PAD	Primary Anastomosis (%)	Colon Esophagus (%)	Total (%)
No inflammation	7 (20)	1 (17)	8 (20)
Mild inflammation	5 (14)	2 (33)	7 (17)
Severe inflammation	23 (66)	3 (50)	26 (63)
Total	35 (100)	6 (100)	41 (100)
Endoscopy, trachea			
No inflammation	22 (63)	4 (67)	26 (63)
Mild inflammation	11 (31)	1 (16)	12 (29)
Severe inflammation	2 (6)	1 (16)	3 (7)
Total	35 (100)	6 (99)	41 (99)

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Author/Year	Study Type	Number of Patients Patient Characteristics	Symptoms	pH Metry	Gastric Emptying Study	Endoscopy	Manometry	Pulmonary Functions Tests	Conclusion
Biller et al 1987 (64)	Case cohort Study	12 EA Patients Mean age 26 yrs (22-31) 3M, 9F All had Type C EA Repair (2-7) days No anastomotic leak Dilatation (0-11)/pt Dilatations done in 8pts Of 40 dilatations. 30 in first decade, 8 in second decade and 2 in third decade 2 had fundoplication for distal stricture in 1 and Barrett;s in 1 2 smoked Minimal alcohol No medications apart from PRN antacids **Contrast study** Patent anastomotic site 10Narrowing in mid esophagus 2 Distal stricture 1 Hiatal hernia 2	Dysphagia 11 Heartburn 9 Choking 4 Vomiting 2 Abdominal Pain 2 Chronic cough 2 Recurrent pneumonia 1 Wheezing 0	9 cases Mean duration 15.5+/-3.3hrs Abnormal in 5/9 (56%) Delayed acid clearance 6 In these 6 Mean number of reflux episodes 16.2+/-8.9 Reflux Index 6.1+/-4.3 Longest episode 21.1+/-7.2min 5/7 patients with heartburn had abnormal acid clearance Esophagitis in 2/6 with delayed clearance 5/6 had heartburn 2/6 had delayed gastric emptying	11 cases 4 abnormal (>70% residual technetium at 60min) GER seen in 4 No aspiration 2/3 with delayed gastric emptying had delayed acid clearance on pH Metry Only 40% with abnormal pH Metry had GER in technetium scan	12 cases Histology Esophagitis 4 80% of those with esophagitis had heartburn 71% of those without esophagitis had heartburn 2/3 patients with esophagitis had delayed acid clearance on PH Metry Barrett's 1	12 cases Mean LES pressure was 21.3+/-2.8mmHg 2 had LES pressure <15mmHg These 2 patients with low LES Pressure also had esophagitis Complete relaxation of LES in 10/12 Amplitude of contraction was low throughout esophagus (compared to historical controls) Lack of peristalsis in at least 1 portion of esophagus seen in all patients Peristalsis seen in upper esophagus in 3 Mid esophagus in 1 Distal esophagus in 4 Most had diffuse abnormality Duration of contraction waves was normal (2-4sec) Men resting pressure of UES was normal and it relaxed normally with pharyngeal contraction Esophagitis did not influence motility abnormalities Esophageal manometry results shown in Table 3	9 cases Mean TLC was 84% of predicted (<80% of predicted in 4) Mean VC was 77% of predicted (<80% of predicted in 5) This was consistent with mild restrictive disease Mean FEV1 was 78% of predicted (<80% predicted in 5) Mean MMFR was 66% of predicted No evidence of airflow obstruction The mean FEV1/VC ratio was 0.82 or 100% of predicted It was >80% predicted in all No correlation between pathological GER (abnormal pH Metry or esophagitis) and abnormal spirometry 3/7 with GER had normal pulmonary function tests ½ without GER had had abnormal pulmonary function Mean decrease in FEV1 in response to co0l air challenge was 5.3% and <15% in all subjects tested. Hence no airway hyperactivity was seen.	Significant symptoms as well as manometric and pulmonary function abnormalities persist into adulthood Increased GER was seen in 67% Low LES pressure seen in 17% and amplitude of contraction was low in all patients however duration of contraction was normal. There was no evidence of cricopharyngeal incoordination. Abnormal peristalsis could contribute to delayed acid clearance and risk of esophagitis Restrictive defect seen in lung function tests, but no reversible airway obstruction was seen. This could be because no episodes of aspiration were seen in scintigraphy. Most adults have dysphagia probably related to dysmotility of esophagus characterized by low amplitude normal duration non peristaltic waves. The heartburn was presumably related to abnormal acid clearance due to manometric abnormality in esophageal body rather than weak LES

									Due to their risk for developing esophagitis EA patients need to be followed up and treated appropriately Although they have mild restrictive defect in lung function airflow obstruction is not seen and they are largely asymptomatic from a respiratory point of view.

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Symptoms	pH Metry	Manometry	Endoscopy	Conclusion
Tovar et al 1995 (65)	Case cohort study	22 EA patients Male : Female 1:4 Age 17.1+/-4.5yrs (9-26) All Type C EA Grossly symptomatic patients and those with prior fundoplication were excluded Historical controls used	Dysphagia 16 (72%) Heartburn 13 (59%) Foreign body impaction 10 (45%) Vomiting 7 (31%) Recurrent chest infection 7 (31%) Nocturnal cough 6 (27%) Pneumonia 3 (13%) Wheezing 3 (13%)	Variables looked at: Reflux Index Number of GER episodes Duration of longest episode Number of episodes>5min Patients with Long nocturnal GER episodes (excluding 2hrs post cibal) ZMD>/=4.5min were considered "Refluxers" regardless of RI GER detected in 12 (54.5%) and ruled out in 10 (45.5%) RI was 10.08+/-7.3% vs 1.06+/-0.8% Number of GER episodes was 29.08 +/- 27.6 vs 4.5 +/- 3 Episodes>5min was 4.4+/-4.1 vs 0.9+/-0.9 Longest episode 43.2+/-27.8 vs 5.9+/- 5 All p<.05 For 11 patients GER was diagnosed on basis of RI 1 it was diagnosed based on ZMD All but 2 had respiratory pattern of long nocturnal episodes which were difficult to clear No alkaline reflux 2 had duodenogastric reflux 5 of refluxing patients (41%) had esophagitis, 1 of which was severe	24 hour Manometry **Variables looked at:** **Contractile activity:** Number of motor sequences/24hr Number of motor sequences/24hr and per minute Motor sequences/min during meals Motor sequences/min in supine position Wave amplitude Wave duration **Propulsive activity:** Peristaltic sequences in 24hr Peristaltic sequences during meals Peristaltic sequences in supine position Ability to clear refluxed acid: Ineffective sequences in 24 hours Ineffective sequences during meals Ineffective sequences in supine position **Table 2 shows manometric data in EA patients and historical controls** EA patients have high number of contractions that like controls have three fold increase with meals, with slowing at night Amplitude and duration of waves was lower than controls	Motor behavior was identical in patients with and without esophagitis	First study to look at 24 hour ambulatory manometry in EA patients Wave amplitude was lower and wave duration in EA patients was shorter than healthy young adults revealing less powerful esophageal contractions. Although motor activity was increased during meals it was almost absent during sleep. Propulsive activity was disorganized and peristaltic sequences <50% even at meal times. They did not extend throughout the esophagus and clearing capacity was absent. Ineffective waves were nearly 100% at all time periods and in all positions Groups with and without GER had identical manometry suggesting that dysmotility was a primary event rather than being due to esophagitis or acid reflux Clearance of refluxed fluid takes place due to gravity in EA patients as they don't have an effective peristaltic pump GER occurred in >50%. The presence of long nocturnal episodes of GER and long ZMDs suggests that GER is responsible for respiratory symptoms GER in EA does not have a benign course given the lack of effective peristaltic pump in the presence of failing LES. Structural abnormalities make these patients a poor candidate for prokinetics, hence anti reflux surgery should be considered in symptomatic EA patients

					Peristaltic activity sequences did not reach 50% of total for any of the 3 periods analysed Complete peristaltic waves involving full length of esophagus was <20% even during meals Simultaneous sequences were seen Failure of clearing capacity of esophagus was seen Proportion of ineffective sequences approached 100% in all patients and for all periods analysed Manometry in patients with and without GER did not differ significantly Trend towards poorer wave quality in those with GER Esophageal motor activity was uniformly disorganized and unable to achieve clearance without apparent relationship to presence or absence of GER **Table 3 shows manometric data in those with and without GER**		with GER and histological esophagitis despite poorer outcome compared to other groups with GER due to inherent dysmotility as fundoplication reduces risks associated with chronic esophagitis

Table 2. 24-Hour Esophageal Manometry Data for 22 TEF Patients and in Several Groups of Normal Adults

	Present Series (TEF) (n = 25)	Stein and DeMeester[10] (Normal Adults) (n = 25)	Emde et al[9] (Normal Adults) (n = 24)	Timmer et al[11] * (Normal Adults) (n = 24)
Contractile activity				
Motor sequences in 24 h (n)	751.6 ± 500.2			1,054
Motor sequences in 24 h (n/min)	0.53 ± 0.35			0.71
Motor sequences during meals (n/min)	1.9 ± 1.1			
Motor sequences in supine position (n/min)	0.28 ± 0.2			
Wave amplitude (mm Hg)				
Upper esophagus	30.5 ± 12.5			
Middle esophagus	32 ± 7.7	39.5 ± 3.9		
Lower esophagus	35 ± 7.6	46.6 ± 3.1	54.5 ± 16	42.03
Wave duration (s)				
Upper esophagus	1.3 ± 0.2			
Middle esophagus	1.6 ± 0.3	2.9 ± 0.1		
Lower esophagus	1.8 ± 0.3	3.4 ± 0.2	3.86 ± 0.5	2.15
Propulsive activity				
Peristaltic sequences in 24 h (%)	44 ± 18.1		53 ± 11.6	49.4
Complete (%)	13.3 ± 5.6			
Peristaltic sequences during meals (%)	48.7 ± 19.8	75.3 ± 4.2		62.1
Complete (%)	18.3 ± 7.3			
Peristaltic sequences in supine position (%)	45.6 ± 22.6	54.5 ± 6	35.2 ± 14.4	37.1
Complete (%)	10.4 ± 9.8			
Clearing capacity				
Ineffective sequences in 24 h (%)	94.1 ± 3.8			
Ineffective sequences during meals (%)	90.4 ± 5.76			
Ineffective sequences in supine position (%)	95.7 ± 4.2			

NOTE. Data are expressed as mean ± SD.

*Some of these figures were recalculated from the original data, and they are expressed without deviations, which could not be calculated.

Table 3. 24-Hour Esophageal Manometry Data for Patients With Nonrefluxing and Refluxing TEF

	Nonrefluxing (n = 10)	Refluxing (n = 12)
Contractile activity		
Motor sequences in 24 h (n)	859 ± 594	661 ± 411
Motor sequences in 24 h (n/min)	0.6 ± 0.4	0.48 ± 0.3
Motor sequences during meals (n/min)	2.1 ± 1.5	1.7 ± 0.8
Motor sequences in supine position (n/min)	0.32 ± 0.23	0.25 ± 0.18
Wave amplitude (mm Hg)		
Upper esophagus	33.8 ± 17.1	27.8 ± 6.6
Middle esophagus	34.9 ± 10	29.7 ± 4.5
Lower esophagus	38.9 ± 8.2	31.8 ± 5.3*
Wave duration (s)		
Upper esophagus	1.3 ± 0.2	2.9 ± 0.1
Middle esophagus	1.7 ± 0.4	1.5 ± 0.1
Lower esophagus	1.8 ± 0.3	3.4 ± 0.2
Propulsive activity		
Peristaltic sequences in 24 h (%)	42.3 ± 20.6	45.4 ± 16.6
Complete (%)	14.2 ± 5.8	12.7 ± 5.7
Peristaltic sequences during meals (%)	46.9 ± 20.7	50.2 ± 19.8
Complete (%)	17.9 ± 6.6	18.7 ± 8.1
Peristaltic sequences in supine position (%)	41.7 ± 21	48.9 ± 24.3
Complete (%)	12 ± 11.9	9 ± 8.1
Clearing capacity		
Ineffective sequences in 24 h (%)	94 ± 3.8	94.1 ± 3.9
Ineffective sequences during meals (%)	91.1 ± 5.2	89.9 ± 6.3
Ineffective sequences in supine position (%)	95.3 ± 4.9	96 ± 3.7

NOTE. Data are expressed as mean ± SD.
*$P < .05$.

GER in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Impedance Reflux Results	Impedance swallow/motility Results	Conclusion
Di Pace et al (66) 2011	Prospective Case control study 2008-2009	**Group 1 (EA)** 15 EA patients Mean age 7.5yrs (5-10yr) 7F, 8M All Type C EA Primary anastomosis without tension No operative complications No associated malformations No prior fundoplications 60% were asymptomatic 26% had dysphagia 14% had retrosternal pyrosis None has respiratory symptoms All had endoscopy 1 month prior to pH-MII study Contrast study done in symptomatic pts with no stricture seen **Group 2 (Control)** 15 Children with suspected GER Mean age 8.3yrs 8F, 7M No patient was on ARM at time of impedance	**Group 1 (EA)** Av 72.1 RBM by MII 26.8 pH only episodes Av 10.6 re-reflux episodes Proximal migration of RBM 95.6% Median MACT 552.9sec Median MBCT 59.9sec All had Reflux Index >6% by pH probe In 2 pts with pyrosis SI >85% In 4 pts with dysphagia no correlation with acid reflux **Group 2 (Control)** Negative pH-MII analysis for both acid and nonacid GER despite symptoms All reflux parameters were normal. No correlation between symptoms and reflux **Results shown in Table 1**	Esophageal Function assessed by: MII swallows of 5mls NS Parameters calculated: **TBTT:** Total bolus transit time **BPT**: Bolus presence time **STT:** Segmental transit time **TPV**: Total propagation velocity As there are no normal values for children, results were compared with those described for adult patients **Results shown in Table 2** 7 swallows showed complete bolus transit in Group 1 (EA) All 10 swallows showed complete bolus transit in Group 2 (Control) In pts with acidic GER, median BPT at each measuring site was significantly longer (p<.001) than values reported in patients without reflux The median TBTT was significantly shorter in pts without reflux when compared to EA children (p<.001) The median STT between each measuring site was significantly shorter in control pts without reflux than in EA pts with acid reflux The TPV was significantly shorter in EA pts than in pts without reflux, p<.001 EA Patients with longer values for TBTT, STT and BPT, the degree of reflux being equal had more symptoms Hence there was a correlation between presence of symptoms and esophageal dysmotility	First study to look at impedance parameters of esophageal motility in healthy children and in patients with EA using only pH-MII Homogenous cohort of EA patients, 5 yrs or older. Patients with endoscopic esophagitis, non acid reflux history of fundoplication were excluded Comparison with control group who had negative pH-MII results In EA patients MACT and MBCT were pathologically prolonged Results of MII Swallow in healthy control children similar to that reported in MII-manometry studies healthy adults Motility results using MII in EA cohort was similar to that reported using manometry All described reflux and motility parameters were more altered in EA cohort compared to healthy controls, consistent with GER and impaired bolus transit in EA patients Impaired motility patters and severe acid GER seen in asymptomatic EA children. Hence authors advocate evaluation of all EA patients regardless of symptoms Authors plan to look at , role of non acid reflux on motility and correlation between endoscopic severity of esophagitis and motility on MII in future as these aspects were not looked at in this study Authors feel MII can be used to test esophageal function by evaluating bolus transit They also feel pH-MII should be used as a preoperative assessment tool in EA patients being considered for fundoplication not only to assess reflux but also to evaluate esophageal dysmotility and select appropriate surgical technique pH-MII can also be used to evaluate efficacy of PPI therapy

Table 1 Impedance reflux parameter

Parameters	Group 1 (EA)		Group 2 (control)		*P*
	Mean (±SD)	Range	Mean (±SD)	Range	
Number of reflux	72.1 (19.1)	39-102	2.1 (3.4)	0-11	<.005
Number of high reflux	69.0 (18.1)	37-96	0.5 (1.2)	0-4	<.005
Number of pH only	26.9 (10.4)	13-45	0.4 (0.6)	0-2	<.005
Number of re-reflux	10.6 (3.5)	5-18	0.2 (0.4)	0-1	<.005
Number of GER correlated symptoms	59.2 (16.7)	36-90	0.1 (0.2)	0-1	<.005
MACT (s)	552.9 (121.6)	356-749	76.8 (20.3)	35-105	<.005
MBCT (s)	59.9 (11.3)	35-82	10.9 (3.8)	5-20	<.005

Table 2 Impedance motility parameters for liquid swallows

Parameters	Group 1 (EA)		Group 2 (control)		*P*
	Mean (±SD)	Range	Mean (±SD)	Range	
TBTT (s)	12.8 (0.4)	12.0-13.4	6.9 (0.7)	6.1-8.3	<.005
BPT (s)					
at Z1	6.9 (0.2)	6.5-7.6	1.8 (0.6)	1.3-3.0	<.005
at Z2	7.2 (0.3)	6.6-7.7	2.1 (0.5)	1.6-3.2	<.005
at Z3	7.8 (0.6)	6.8-9.0	2.6 (0.5)	1.9-3.4	<.005
at Z4	8.4 (0.8)	7.3-9.9	3.3 (0.5)	2.4-4.0	<.005
at Z5	9.5 (0.9)	8.3-10.8	4.5 (0.5)	3.7-5.2	<.005
at Z6	11.0 (0.5)	10.4-11.9	5.7 (0.6)	4.7-6.6	<.005
Segment transit time (s)					
STT1 Z1-Z2	3.1 (0.1)	2.8-3.3	0.6 (0.1)	0.4-0.7	<.005
STT2 Z2-Z3	3.2 (0.1)	3.0-3.4	0.7 (0.1)	0.5-0.8	<.005
STT3 Z3-Z4	3.4 (0.1)	3.1-3.6	0.8 (0.1)	0.7-1.1	<.005
STT4 Z4-Z5	3.5 (0.1)	3.3-3.8	1.1 (0.1)	0.9-1.4	<.005
STT5 Z5-Z6	3.7 (0.1)	3.5-4.0	1.4 (0.1)	1.2-1.7	<.005
Total propagation velocity (cm/s)	0.6 (0.1)	0.5-0.8	3 (0.2)	2.8-3.4	<.005

Feeding and Nutrition in EA-TEF

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of patients</th><th>Methods</th><th>Results</th><th>Conclusion</th></tr>
<tr>
<td>Smith et al
1985</td>
<td>Retrospective review of symptoms with use of feeding questionnaire</td>
<td>23 patients all of whom had primary anastomosis</td>
<td>Feeding questionnaire sent to 35 families whose child with EA was operated on by 1 surgeon between 1977-1981</td>
<td>23/35 (66%) response

100% had feeding difficulty
0% strictures
Majority had at least 1 gastroscopy post repair

Type of difficulty
Coughing 14(61%)
Dysphagia 14(61%)
Choking 13(57%)
Vomiting 9(39%)
Retching 5(22%)
More than one difficulty 15(65%)

Food bolus impaction 18(94%)
Managed at home 100%
Drink 17(94%)
Held upside down 17(94%)
Fingers down throat 6(33%)
No endoscopic removal of food bolus impaction required

Age of onset of feeding difficulty
<6months 15 (65%)
8-12months 8 (35%)

Type of food causing feeding difficulty

<table>
<tr><th>Food</th><th>Number (%)</th></tr>
<tr><td>Infant</td><td></td></tr>
<tr><td>Hot drinks</td><td>1(4%)</td></tr>
<tr><td>Cold drinks</td><td>2(9%)</td></tr>
<tr><td>Milk</td><td>2(9%)</td></tr>
<tr><td>Juice</td><td>3(13%)</td></tr>
<tr><td>Packet baby food</td><td>4(18%)</td></tr>
<tr><td>Strained food</td><td>5(22%)</td></tr>
<tr><td>Liquidised food</td><td>5(22%)</td></tr>
<tr><td>Mashed food</td><td>7(30%)</td></tr>
<tr><td>Junior baby food</td><td>10(44%)</td></tr>
<tr><td>Food with lumps</td><td>17(74%)</td></tr>
<tr><td>Stringy food</td><td>17(74%)</td></tr>
<tr><td>Older children</td><td></td></tr>
<tr><td>Biscuits</td><td>6(26%)</td></tr>
<tr><td>Meat</td><td>7(30%)</td></tr>
<tr><td>Cakes</td><td>7(30%)</td></tr>
<tr><td>Fruit</td><td>12(52%)</td></tr>
<tr><td>Bread</td><td>13(56%)</td></tr>
<tr><td>Vegetables</td><td>17(74%)</td></tr>
</table>

10(43%) parents had been warned about feeding difficulty
10(43%) found it difficult to deal with
17(74%) would have liked more advice</td>
<td>Universal prevalence of feeding difficulties post EA repair.

No information given about results of contrast studies or gastroscopies.

Lack of adequate education to parents on how to deal with feeding difficulties especially food bolus impactions.</td>
</tr>
</table>

Feeding and Nutrition in EA-TEF

Author/Year	Study Type	Number of patients Patient characteristics Study Method	Results-Feeding	Results-Growth	Conclusion
Puntis et al 1990	Retrospective review of feeding and growth with use of a questionnaire Case control cohort study	230 questionnaires on feeding history sent out to families belonging to Tracheoesophageal fistula support group in UK 124 EA patients/parents completed the questionnaire Male: Female; 2:1 **Primary anastomosis** 92(74%) Median age 4.3yrs (.5-22.8) Elective dilatations 48(52%) 38(41%) admitted for food bolus impactions **Esophagostomy+gastrostomy followed by esophageal substitution** 32(26%) Median age 5.6yrs (1.3-22.3) P=NS Median age of closure of esophagostomy 1yr(.1-2.5yr) Elective dilatations 12(38%) 10(31%) admitted for emergency endoscopy for food bolus impactions No sig difference between dilatations in both groups (P=NS) **Controls**-50 Children of colleagues/siblings of inpatients Feeding score calculated based on results of questionnaire	**Feeding in hospital** **Primary anastomosis group** 50% parents allowed to feed children in hospital 11% never allowed to do so 50% breast fed for median of 3mths (2wk-21mths) 15% discouraged from breast feeding **Esophagostomy group** 75% parents allowed to feed children in hospital 6% never allowed to do so 38% breast fed for median of 2.5mths (1wk-7mths) Significantly more mothers felt they were discouraged from BF (p=.02) 15% discouraged from breast feeding **General advice** 45% of parents were warned about feeding difficulties at discharge. 1/3 received specific advice. Only 6% saw a dietician. **Specific Feed related difficulties** **Controls** During milk feeds: Slow to feed 12% Coughing/choking with feeds 6% Vomiting 8% Feed refusal 10% Median age at introduction of solids 4mths(2-7) Solid+lumps 8(5-16)	**Primary anastomosis group** Height and weight data on 73pts Stunted 10(14%) Wasted 7 (10%) Stunted and wasted 2 (3%) Mean SD height for age SD -0.5(1.8) Mean SD weight for height SD score -0.4(1.6) Height for age (p=.02) and weight for height(p=.04) compared to normal population **Esophagostomy group** Height and weight data on 27 pts. Stunted 9(33%) Wasted 2 (8%) Stunted and wasted 2 (8%) Higher proportion compared to primary anastomosis gp (p<.05) Mean SD height for age SD -1.78(1.7) Mean SD weight for height SD score -1.1(0.9) Height for age (p<.0001) and weight for height(p<.0001) compared to normal population and compared to primary anastomosis group, p=.002 and .01 respectively Prevalence of growth retardation did not decrease with increasing age in either group	A third of patients had symptoms of coughing, choking, vomiting and feed refusal in the 1st year, which was significantly higher than controls. Number of symptom free subjects increased with age with two thirds being symptom free by age 7 High prevalence of growth failure in both groups, with both being significantly below reference population for height for ager and weight for height. No negative correlation between feed scores and nutritional state. Follow up was only available for 50% of patients in a group at a time. No data on endoscopies, pH studies, contrast studies given.

			Prevalence of symptoms decreased with introduction of solids: Slow to feed 4% Coughing/choking with feeds 2% Vomiting 2% Feed refusal 4% By 1yr symptoms had resolved in 74% By 2yrs 90% were symptom free. **Primary anastomosis group** During milk feeds: Slow to feed 61% Coughing/choking with feeds 32% Vomiting 17% Feed refusal 20% Compared to controls feeds refusal and vomiting not different (P=NS) Slow to feed (p<.01), coughing/choking (p=.0002) increased. Median age at introduction of solids 6mths(1.5-30) Solid+lumps 12(2-54) Introduction of solids was delayed compared to controls (p<.0001) All symptoms related to solid foods more common compared to controls: Slow to feed (p<.0001) Coughing/choking with feeds (p<.0001) Vomiting (p=.007) Feed refusal (p=.02) By 1yr (88 F/U)symptoms had resolved in 20% By 7yrs (21 F/U) 57% were symptom free		

			Esophagostomy group During milk feeds: Slow to feed 38% Coughing/choking with feeds 19% Vomiting 31% Feed refusal 22% Significantly fewer were slow feeders compared to primary anastomosis (<.05) Compared to controls feeds refusal and coughing not different (P=NS) Slow to feed and vomiting (p<.01)) increased. Median age at introduction of solids 12mths(3-24) Solid+lumps 18(9-48) Introduction of solids was delayed compared to controls (p=.0003) and primary anastomosis gp (.001 for blended solids and .04 for solids with lumps) With solids: Slow to feed 50% Coughing/choking with feeds 28% Vomiting 31% Feed refusal 19% All symptoms related to solid foods more common compared to controls: Slow to feed (p<.0001) Coughing/choking with feeds (p=.0007) Vomiting (p=.0002) Feed refusal (p=.04) By 1yr symptoms had resolved in 0% By 7yrs (12 F/U) 66% were symptom free Troublesome foods: Meat 37% Apple 23% Bread 23% Oranges 14% Raw veg 12% **Dysphagia** with certain		

			foods : Primary anastomosis 26% Esophagostomy 6% (p<.01) **Feeding Score:** Primary anastomosis 16(0-42) Esophagostomy 13 (0-48), p=NS Comparing growth retarded with normal children (p=NS) Feeding scores did not correlate with height for age or weight for height SD scores **Advice for parents:** 11% discussed feeding problem with medical personnel A third discussed with dietician		

Feeding and Nutrition in EA-TEF

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of patients

Patient characteristics

Study Method</th><th>Results</th><th>Conclusions</th></tr>
<tr>
<td>Andrassy et al

1983</td>
<td>Retrospective review</td>
<td>53

Age

Mean 9yr4mths (10.5mths-31yrs)

29M, 24F

EATypes

Type A 2

Type B 3

Type C 44

Type D 1

Type E 3

Nutritional Assessment

Birth weight

Current weight

Current Height

Triceps skin fold (TSF)

Mid arm circumference (MAC)

Arm muscle circumference=MAC-0.314(TSF)

Weight for height used as indicator of acute malnutrition

Height for age as indicator of chronic malnutrition</td>
<td>
<table>
<tr><th></th><th>Ht/Age %</th><th>Wt/Ht %</th><th>TSF %</th><th>MAMC %</th></tr>
<tr><td>Minus 1SD</td><td>11.3</td><td>18.9</td><td>7.5</td><td>28.3</td></tr>
<tr><td>Minus 2SD</td><td>18.9</td><td>5.7</td><td>1.8</td><td>5.7</td></tr>
</table>
<table>
<tr><th></th><th>Ht/Age -1SD -2SD %</th><th>Wt/Ht -1SD -2SD %</th><th>TSF -1SD -2SD %</th><th>MAMC -1SD -2SD %</th></tr>
<tr><td><2500gm 16</td><td>18.8 16.8</td><td>25 6.25</td><td>6.25 6.25</td><td>31.2 12.5</td></tr>
<tr><td>>2500gm 37</td><td>8.1 18.9</td><td>16.2 5.4</td><td>8.1 8</td><td>27 2.7</td></tr>
</table>
No significant difference between groups for data
</td>
<td>LBW did not effect on subsequent development as there was no significant difference in acute or chronic malnutrition data between <2500 and >2500gms BW groups

Under 5 and >5yrs compared as those operated on after 1975 received TPN in post-operative period. But as there was no significant difference between groups, there was no significant effect of advanced nutritional support during early hospitalisation

Effect of catch up growth more obvious >13yrs. Prevalence of chronic malnutrition decreased in this group. ? This due to decreased GERD and less strictures and less dysphagia with age.</td>
</tr>
</table>

Comparisons:

BW<2500gm vs >2500gms

<5yr vs >5yrs

<13yrs vs >13 yrs

	Ht/Age -1SD -2SD %	Wt/Ht -1SD -2SD %	TSF -1SD -2SD %	MAMC -1SD -2SD %
<5yrs 16	6.25 25	18.7 6.25	12.5 0	18.75 6.25
>5yrs 37	13.5 16.2	18.9 5.4	5.4 2.7	32.4 5.4

No significant difference between groups for data

	Ht/Age -1SD -2SD %	Wt/Ht -1SD -2SD %	TSF -1SD -2SD %	MAMC -1SD -2SD %
<13yrs 40	12.5 22.5	25 5	7.7 2.5	25 7.5
>13yrs 13	7.7 7.7	0 7.7	7.7 0	38.5 0

			Patients less than 13yrs had greater prevalence of chronic malnutrition (Ht/Age), p=.06 and acute malnutrition (Wt/Ht) No statistically significant difference between groups, but higher prevalence of acute and chronic malnutrition in <5yr group Several malnourished pts. had dilatations for strictures	

	Ht/Age -1SD -2SD %	Wt/Ht -1SD -2SD %	TSF -1SD -2SD %	MAMC -1SD -2SD %
<5yrs	6.25	18.7	12.5	18.75
16	25	6.25	0	6.25
>13yrs	7.7	0	7.7	38.5
13	7.7	7.7	0	0

Feeding and Nutrition in EA-TEF

Author/Year	Study Type	Number of patients Patient characteristics	Results	Conclusions
Kimble et al 1999	Retrospective Review Case Series	9 Type A, EA babies between 1979-1996 All had gastrostomy Median gestational age 37wk(33-41) Median BW 2550gm (1540-3530)	After initiation of feeds 7(78%) developed complications 2 posterior gastric perforations (1 fatal) 1 leak at gastrostomy site into peritoneal cavity 1 wound dehiscence with infection 1 gastrostomy wound infection 1 NEC No relationship between complications and gestation or BW or presence of other malformations Both perforations occurred in prems (33wk/32wk), but they were not SGA	High complication rate post gastrostomy feeding in neonates with pure EA. Caution should be used whilst introducing gastrostomy feeds which should be graded up slowly. Prophylactic antibiotics might be helpful. EA patients have small abnormal stomach that is vulnerable to damage during surgery and not capable of handling large feeds volumes. ? This because the stomach has not been exposed to the maturing effects of amniotic fluid containing trophic substances (IGF1 and 2 and EGF) in utero. Amniotic fluid may also help in increasing gastric capacity/size

EoE in EA-TEF

<table>
<tr><th>Study Author/Year</th><th>Study Type</th><th>Number of patients</th><th>Patient characteristics</th><th>Follow up</th><th>Symptoms</th><th>Endoscopy</th><th>Barium Swallow

pH Probe</th><th>Treatment</th><th>Conclusion
Other remarks</th></tr>
<tr>
<td>Oliveira et al/2008</td>
<td>Retrospective case series</td>
<td>EE (>20 eosinophils/HPF) 4

IE (Intermediate esophagitis 5-19 eosinophils/HPF) 4</td>
<td>
<table>
<tr><th></th><th>EE</th><th>IE</th></tr>
<tr><td>Median Age (Range)</td><td>9.8yrs (4-13.4)</td><td>11.2yrs</td></tr>
<tr><td>Patient Environmental Allergy

Asthma

Food Allergy</td><td>75%

75%

75%</td><td>25%

75%

0%</td></tr>
<tr><td>Family history Food allergy</td><td>0%</td><td>50%</td></tr>
<tr><td>Blood results Eosinophilia .5-1/>1</td><td>100%
75%/25%</td><td>33%
0%/100%</td></tr>
</table>
Anaemia in 50% EE and 25% IE

1 in 4 had Type 1 EA in both groups
50% premature in EA, 25% in IA

IE had more malformations than EE
</td>
<td>May2003-January 2007</td>
<td>
<table>
<tr><th>Symptoms</th><th>EE%</th><th>IE%</th></tr>
<tr><td>Dysphagia</td><td>100</td><td>100</td></tr>
<tr><td>Vomiting</td><td>50</td><td>25</td></tr>
<tr><td>GERD</td><td>100</td><td>100</td></tr>
<tr><td>Chest pain</td><td>25</td><td>50</td></tr>
<tr><td>Epigastric pain</td><td>0</td><td>25</td></tr>
<tr><td>FTT</td><td>25</td><td>25</td></tr>
<tr><td>Constipation</td><td>0</td><td>50</td></tr>
<tr><td>Stricture Needing dilatation</td><td>50</td><td>25</td></tr>
</table>
</td>
<td>
<table>
<tr><th></th><th>EE%</th><th>IE%</th></tr>
<tr><td>Endoscopy
Difficulty passing Scope</td><td>50</td><td>0</td></tr>
<tr><td>Normal</td><td>0</td><td>25</td></tr>
<tr><td>Furrows</td><td>75</td><td>66</td></tr>
<tr><td>White plaques</td><td>50</td><td>33</td></tr>
<tr><td>Pale</td><td>25</td><td>0</td></tr>
<tr><td>Hiatal hernia</td><td>0</td><td>25</td></tr>
<tr><td>Gastritis</td><td>25</td><td>25</td></tr>
<tr><td>Duodenitis</td><td>25</td><td>0</td></tr>
<tr><td>Histology
Eosinophilic abscess</td><td>25</td><td>0</td></tr>
<tr><td>Degranulated eosinophils</td><td>50</td><td>0</td></tr>
<tr><td>Elongated papillae</td><td>50</td><td>25</td></tr>
<tr><td>Gastritis</td><td>50</td><td>75</td></tr>
<tr><td>Duodenitis</td><td>25</td><td>0</td></tr>
<tr><td>HPylori</td><td>0</td><td>0</td></tr>
<tr><td>GERD</td><td>75</td><td>75</td></tr>
</table>
</td>
<td>Barium Showed dysmotility

75% EE
50%

pH Probe Abnormal

75% EE
100% IE</td>
<td>PPI
Effective in 67% EE
75% IE

Prokinetics
Not effective

Steroids
Swallowed inhalation
Or
Systemic

100% effective in both groups

Moteleukast
Reduced symptoms 4/4EE
1/1IE but all these pts needed steroids at some stage

Diet modification not done</td>
<td>Consider EE if ?GERD symptoms or dysphagia Refractory to treatment

High incidence of environmental and food allergies in EE group

Although EE is diagnosed on biopsy efficacy of treatment is reported based on symptoms and not repeat endoscopy and biopsy

GERD signs mentioned in biopsy but not what they are

Specific tests (SPT/Patch) for allergy not done

Diet not used in treatment

PPI mentioned as being effective but PPI responsive hyper eosinophilia can only be diagnosed on biopsy so improvement could be due to GERD</td>
</tr>
</table>

									Whether patients were on PPI at time of diagnosis not mentioned How is difficulty passing scope different to a stricture?

EoE in EA-TEF

Study Author/Year	Study Type	Number of patients	Patient characteristics	Follow up	Symptoms	Endoscopy	Barium Swallow pH Probe	Treatment	Conclusion Other remarks
Gorter et al 2012	Retrospective review Case series	2	Patient 1 10yrs, F Patient 2 15yrs, M Both Type C EA-TEF Blood tests Eosinophilia 100%	Patient 1 17yrs Patient 2 26yrs	Dysphagia 100% Epigastric pain 100% Environmental allergy 50% Food allergy 100%	>20eosinophils/HPF 100% at age 10yrs in patient 1 and age 15yrs in patient 2 At age 6 grade 2 GERD in patient 1 At age 4 severe GERD in patient 2 Barrett's with gastric metaplasia seen in patient 2 at age 15yrs	No stricture in barium At age 6 abnormal pH study in patient 1 At age 4 abnormal pH study in patient 2	Dilated in absence of stricture before diagnosis made Patient 2 had fundoplication at age 5 but symptoms persisted Efficacy of treatment PPI 1/2 Local/systemic steroids 1/2 Dietary modification 1/2	Incidence of 1 in 80 amongst EA patients in this center in this retrospective review Consider EoE if GERD symptoms and dysphagia refractory to anti reflux treatment before considering fundoplication

Study Author/Year	Study Type	Number of patients	Patient characteristics	Follow up	Symptoms	Endoscopy	Barium Swallow pH Probe	Treatment	Conclusion Other remarks
Batres et al 2002	Case series	3	2M, 1F **Time of diagnosis of EoE** Patient 1 -28months Patient 2-2yrs Patient 3- 1yr8months **Diet prior to EoE diagnos**is Patient 1 protein hydrolysate formula for vomiting at time of discharge post EA repair. At age 1 was on normal diet Patient 2 soy formula at discharge Patient 3 normal diet **Allergies** Reactive airway disease 2/3 Environmental 2/3 Food 2/3 Eosinophilia 1/3	Patient 1 no recurrence of stricture at 5yr F/U on diet Patient 2 no recurrence of stricture at 3.5yr F/U on diet Patient 3 no recurrence of stricture at 3yr F/U on diet	Vomiting 2/3 Dysphagia 3/3 FTT 1/3	Endoscopy Furrows 0% Stricture 100% Biopsy >20eosinophils/HPF 100%	Strictures in barium 3/3	PPI 3/3 Injection of steroids into stricture 1/3 Dietary modification 3/3	Consider EoE in recurrent stricture in EA-TEF All patients here were treated with dilatation, maximal PPI therapy and diet modification for EoE

EoE in EA-TEF

Study Author/Year	Study Type	Number of patients	Patient characteristics	Follow up	Symptoms	Endoscopy	Barium Swallow pH Probe	Treatment	Conclusion Other remarks
Yamada et al 2013	Retrospective review Of biopsies of EA and CS between 2005-2012	6 4 (EA) 1 (EA + Congenital stenosis CS) 1 CS	4M, 2F Age at biopsy 3.7yrs (6mths-14yrs) EA 5 Type A 2 Type C 3 CS 1 CS + EA 1 Patient allergy Food 4 Asthma+ Allergic rhinitis 1 Atopic dermatitis 1 Family allergy Food 2 Food + allergic rhinitis 2 Allergic rhinitis 1 Atopic dermatitis 1 Blood results Raised IgE2/6 Eosinophilia 0% RAST Food 1 Food + pollen 2 Environmental 1	2 lost to F/U	Nausea/vomiting 3/6 Regular dilatation 2/6 Recurrent Fever 1/6	Endoscopy (5) Stricture 5 Furrowing 0 Exudate 0 Circumferential inflammation 2 Erosion 1 Scarring 1 Histology <15eos/HPF 1 15-50eos/HPF 3 >100eos/HPF 2 Raised lymphocytes 5 Raised neutrophils 4 Raised plasma cells 2 Repeat endoscopy (3) Reduction in number of eosinophils 3/3	Barium showed severe reflux 1	Dilatation +PPI 3 Dilatation +PPI+ steroids (systemic and intralesional)1 Dilatation only 1 Diet modification in combination with other therapy 2 Surgery 1 (Bianchi) Short term improvement 6/6 3 had subsequent fundoplication 1 with CS alone had resection and anastomosis	EoE increases risk of strictures in EA Male predominance High incidence of food allergies which may be cause eosinophilic infiltration in EA/CS resulting in strictures Dilatation +PPI +/- steroids effective treatment

EoE in EA-TEF

<table>
<tr><th>Study Author/Year</th><th>Study Type</th><th>Number of patients

Follow up</th><th>Patient Characteristics</th><th>Symptoms</th><th>Endoscopy</th><th>Stricture</th><th>Surgery</th><th>Treatment</th><th>Conclusion
Other remarks</th></tr>
<tr>
<td>Dhaliwal et al
2013</td>
<td>Retrospective review</td>
<td>113 EA patients
18 EoE
85 non EoE

10 lost to F/U and excluded from study

13 yr follow up of 103 patients</td>
<td>
<table>
<tr><th></th><th>EoE</th><th>No EoE</th></tr>
<tr><td>M:F</td><td>1:1.6</td><td>1:1.3</td></tr>
<tr><td>Gestation</td><td>37 (32-41)</td><td>38 (28-41)</td></tr>
<tr><td>Cardiac</td><td>3 (17%)</td><td>11(13%)</td></tr>
<tr><td>Vertebral</td><td>2(11%)</td><td>8(9%)</td></tr>
<tr><td>Anal</td><td>2(11%)</td><td>10(12%)</td></tr>
<tr><td>Type of EA</td><td>Type C 17(94%)
Type A 1(6%)</td><td>Type C 74 (87%)
Type A 9(11%)
Type B 1(1%)
Type H 1(1%)</td></tr>
</table>
P=NS when comparing EA/EoE with EA/no EoE groups

Median age of diagnosis of EoE was 1yr and 6 mths
(8mths-8yr and 7mths)

EoE group
Atopy condition 89 (50%)
Asthma 7(38%)
Food 6 (33%)
Eczema 3 (17%0

Blood Results
RAST done in 9, 6/9(67%) +ve
SPT done in 3, 3/3 (100%) +ve
Main allergens-dairy,egg,peanut
</td>
<td>
<table>
<tr><th></th><th>EoE (%)</th><th>No EoE (%)</th><th>P</th></tr>
<tr><td>Reactive Airway Disease</td><td>11 (61%)</td><td>9 (10%)</td><td><.0001</td></tr>
<tr><td>Hypoxic spells</td><td>4 (22%)</td><td>4 (5%)</td><td>.03</td></tr>
<tr><td>GERD</td><td>12 (67%)</td><td>14 (16%)</td><td><.0001</td></tr>
<tr><td>Dysphagia</td><td>10 (56%)</td><td>8 (9%)</td><td><.0001</td></tr>
<tr><td>Food Impaction</td><td></td><td></td><td>NS</td></tr>
<tr><td>Chest Infections</td><td></td><td></td><td>NS</td></tr>
<tr><td>Tracheomalacia</td><td></td><td></td><td><.0001</td></tr>
</table>
</td>
<td>EoE diagnosed if >15 eosinophils/HPF

10(56%) had:
furrows
white plaques
mucosal rings

Median number of eosinophils 30/HPF
(19-80/HPF)

Hyalinisation 86%
Basal cell hyperplasia 100%

Distribution
Diffuse 10(56%)
Focal 8(44%)

Location
Proximal 1(6%)
Distal 5(28%)
Proximal and distal 12(67%)

Progress endoscopy on trt was done in 17/18 , 95%

Complete histological resolution seen in 11/17, 65%
Of these:
PPI 45%
PPI+steroids 45%
PPI + diet 10%</td>
<td>7(38%) had stricture at time of diagnosis of EoE

4 were dialated endoscopically
2 resolved on trt of EoE
1improved on trt of EoE but was also dilated

Age at stricture diagnosis
<table>
<tr><th></th><th>EoE</th><th>No EoE</th><th>P</th></tr>
<tr><td>Long Gap</td><td>5 (28%)</td><td>2 (2%)</td><td>.001</td></tr>
<tr><td><1yr</td><td>8 (44%)</td><td>25 (29%)</td><td>NS</td></tr>
<tr><td>>1yr</td><td>8(44%)</td><td>13 (15%)</td><td>.009</td></tr>
</table>
In EA pts, having LG or EoE or both increased risk of developing strictures (relative risk 1.9)

EA pts with LG had increased risk of dev EoE (relative risk 11.8)

Having LG and EoE in EA pts increased risk of developing stricture 4:1
</td>
<td>
<table>
<tr><th>Surgery</th><th>EoE</th><th>No EoE</th><th>P</th></tr>
<tr><td>Aortopexy</td><td>4(22%)</td><td>5(6%)</td><td><.0001</td></tr>
<tr><td>Fundoplication</td><td>5(28%)</td><td>7(8%)</td><td><.0001</td></tr>
<tr><td>Gastrostomy</td><td>6(33%)</td><td>11(13%)</td><td>NS</td></tr>
</table>
</td>
<td>All patients were on PPI at diagnosis of EoE which was continued

11 (61%) were trt with topical steroids (swallowed inhaled fluticasone or budesonide slurry)

6 (33%) were also trt with diets based on RAST or SPT

Symptom improvement 100%</td>
<td>EoE should be considered in EA patients with persistent symptoms despite GERD trt, increasing dysphagia and recurrent strictures.

EoE needs to be excluded in patients with severe tracheomalacia and hypoxic spells

EoE needs to be excluded before doing fundoplication for persistent symptoms.</td>
</tr>
</table>

					Partial histological improvement in 6/17, 35% Of these: PPI+steroids 50% PPI+steroid+diet 50%				

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Results Dysphagia incidence Stricture Incidence Endoscopic Balloon Dilatation of Strictures	Conclusion
Antoniou et al (1) 2010	Retrospective Review 1988-2008	**59 EA patients with strictures** All Type C EA All had primary repair 48 from own hospital 11 from elsewhere 33M, 26F Mean age 10.5months (1-36) Anastomotic leak in 19 GER 23 (39%) All initially treated with medication **Dysphagia** Grade 0 No dysphagia Grade 1 Unable to swallow solids or food impaction Grade 2 Unable to swallow soft foods Grade 3 Only liquids tolerated Grade 4 Unable to swallow liquids For those <8months dysphagia graded on findings on endoscopy or contrast study Treatment was considered effective when dysphagia was grade 0 or 1 >12mths after last dilatation session **Depending on effectiveness children were divided into 2 groups**: Group A Treatment was effective Group B Treatment was ineffective **Response to dilatation**: Excellent when there was no need for dilatation for recurrent strictures Satisfactory when upto 5 dilatations were required Fair when >5 sessions were needed Initially balloon dilatation was done using Rigiflex single diameter balloon catheter In last 8 years over the wire multidiameter CRE balloon catheter was used When patient had symptoms of GER or endoscopic features of GER the 18hr pH Metry was done and anti reflux treatment started	**Stricture Incidence** Overall 56/196 (28.5%) 8/18 (44.4%) of Type A EA 48/167 (28.7%) of Type C EA 0/1 Type B EA 0/1 Type D EA 0/9 Type E EA **Stricture Location** Upper third 5 (8.5%) Middle third 54 (91.5%) Dysphagia Incidence Grade 1 11 (18.6%) Grade 2 33 (55.9%) Grade 3 15 (25.4%) **Balloon Dilatation** Successful in all patients after total of 165 sessions Mean 2.79+/=2.1 (1-9)/patient Patients who were able to swallow liquid (Grade 3) were dilated for mean 5.5 sessions vs those with mild (Grade 1 or 2) dysphagia who needed 1.8 sessions 35.6% achieved symptom relief after single dilatation **Response to dilatation** Excellent 21 (35.6%) Satisfactory 26 (44.1%) Fair 12 (20.3%) Strong correlation between response to dilatation and age, p<.001, r=.71 Strong correlation between grade of dysphagia and number of sessions required for effective treatment, p<.001, r=.8 **Treatment** Effective 47 (79.7%) Ineffective 12 (20.3%0 Mean number of sessions required for relief of dysphagia in Group A (effective group) was 1.8+/-0.8 (1-3), and mean dysphagia grade was 1.9+/-0.6 Mean number of sessions required for relief of dysphagia in Group B (ineffective group) was 6.6+/-0.9 (6-9), and mean dysphagia grade was 2.9+/-0.3	**79.7% efficacy for balloon dilatation of strictures was comparable to that in literature (Table 2)** There is correlation between severity of dysphagia and number of sessions required to achieve adequate dilatation. Important to start dilatations early to reduce scar formation. Therapy was started as early as 4 weeks post EA repair. Patients younger than 6mths required fewer dilatations. 70.9% of patients <6mths required only 1 dilatation for symptom relief and 29.1% required 2 sessions No complications seen after 165 dilatation procedures Hence balloon dilatation is minimally invasive effective and safe first line therapy for the management of anastomotic strictures following EA repair because of it's low complication rate and good clinical outcome In patients with resistant strictures GER should be considered and treated with medication and fundoplication if medication fails Temporary placement of a covered retrievable stent can be considered for resistant strictures

			Significant difference in the rate of effective treatment between those with dysphagia Grade <2 (44/45, 97.7%) and those with Grade >2 (4/15, 26.6%), p<.001 All patients with adequate dilatation were younger (mean 8.6+/-6.8mths) than those unresponsive or partially responsive to balloon dilatation (mean 17.9+/-4.7mths) During mean follow up period of 19.5months (12-36) after last dilatation none of the 47 showed recurrent symptoms 1 year after dilatation 97.7% of those with Grade 1 or 2 dysphagia were asymptomatic vs 26.6% of those with a higher grade dysphagia All those with ineffective treatment (12) had GER 7 responded to GER medication 4/12 had fundoplication 1 had retrievable stent ad improved to Grade 1 Number of sessions required was significantly less in those without GER (1.4-4.8)/patient **Complications** No complications of perforation or hemorrhage No mortalities	

TABLE 2. Literature review on balloon dilatation in children with esophageal stricture following EA repair

References	No. patients	Perforation rate, %	Follow-up	Technique
Lang et al (1)	16	1.92	2.5 y	Endosc + Fluorosc
Goldthorn et al (3)	5	0	7 y	Fluorosc
Tam et al (4)	13	0	NR	Endosc + Fluorosc
Sandgren et al (6)	31	0	NR	Endosc + Fluorosc
Lan et al (7)	63	1.58	6.6 y	Endosc + Fluorosc
Fasulakis and Andronikou (11)	10	0	NR	Fluorosc
Kim et al (12)	26	1.75	NR	Fluorosc
Said et al (13)	25	1.7	NR	Fluorosc
Shah and Berman (14)	10	5.8	21 mo	Endosc + Fluorosc
Yeming et al (15)	10	0	42 mo	Fluorosc
Hoffer et al (16)	7	3.8	3 y	Fluorosc
Lisy et al (17)	10	0	NR	Fluorosc
Weintraub and Eubig (18)	33	0.37	NR	Fluorosc
Ko et al (19)	29	10	3.1 y	Fluorosc

Endosc = endoscopy; Fluorosc = fluoroscopy; NR = not reported.

STRICTURE in EA-TEF

Author/Year	Study Type	Number of patients Patient Characteristics Post Operative Complications	Stricture	Conclusion
Aldabbagh et al (2) 2012	Retrospective Review	20 patients 13M 7F Mean Gestational Age 38weeks (36-41) Prematurity 2 (10%) Mean BW 2.9Kg (2.5-4.1) Follow Up mean 4years (2-5) **Complications** Anastomotic Leak 1 (5%) Recurrent TEF 1 (5%)Recurrent LRTI 12 (60%) GER 8 (40%) **Nutrition** 1 Year 25-50th Centile 8 (40%) 10-25th Centile 6 (30%) <10th Centile 6 (30%) 2Year 25-50th Centile 9 (45%) 10-25th Centile 9 (45%) <10th Centile 2 (10%)	Anastomotic stricture defined as narrowing that required dilatation **Anastomotic Stricture 6 (30%)** **Treatment** Balloon Dilatation AND Anti Reflux Therapy (H2Blocker + Domperidone) All 6 patients with stricture had GER and LRTI Successful 4/6 1 had revision of anastomosis + Fundoplication 1 had Fundoplication only	Early detection and treatment of GER is important to reduce post operative stricture rate Treat of anastomotic strictures involves balloon dilatation and GER treatment (medication nor fundoplication) and if needed stricture resection Recurrent respiratory infections were most frequent (60%) in those with strictures Prophylactic post operative esophageal dilatation was not done in this study in patients with no symptoms of stricture (14 patients) and they remained well. Hence authors considered that dilatations for symptomatic strictures is superior to routine dilatations Balloon dilatation for anastomotic stricture was an effective method of treatment in EA patients

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient characteristics	Results of Mitomycin C application to stricture	Conclusion
Uhlen et al (3) 2006	Prospective case cohort study 2001-2004 All had short stenosis<4cms	4 patients with refractory esophageal strictures 2 EA 1M 1F Age 3 and 1year Stricture located 12-15cms above dental arch 4-7 dilatations over 5-24 month period prior to Mitomycin C 2 patients with caustic ingestion	Mitomycin C (1mg/ml) applied locally with rigid esophagoscope for 2 minutes after dilatation using a bougie Followed up for 19-21 months by clinical examination, contrast study and endoscopy Only 1 application required in EA patients Asymptomatic No recurrence of stricture in contrast study No dysplasia in esophageal biopsies	Mitomycin C is an anti neoplastic agent which inhibits DNA synthesis, reduces fibroblastic collagen synthesis by suppressing DNS dependent RNA synthesis and cellular proliferation during the late G1 and S phases of the cell cycle No data exists to date on most effective concentration, duration or frequency of application of Mitomycin C Theoretical risk of secondary malignancy has not been answered and these patients require long term follow up with regular endoscopic examinations Local application of Mitomycin C is a possible alternative to surgery, stent placement or recurrent dilatations in children with recurrent esophageal strictures Large sample size with long term follow up before definitive conclusion can be drawn about usefulness of Mitomycin C in treatment of esophageal strictures in children

STRICTURE in EA-TEF

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of Patients
Patient Characteristics
Methodology</th><th>Results</th><th>Conclusion</th></tr>
<tr>
<td>Upadhyaya et al (4)
2007</td>
<td>Prospective case cohort study
1999-2001</td>
<td>50 consecutive cases of EA-TEF
(Pure EA excluded)

Cases divided into 4 groups based on gap length
Group A: (Ultra long gap) >3.5cms
Group B (Long gap) >2 to <3.5cms
Group C (Intermediate gap) >1 to <2cms
Group D (Short gap) <1cm</td>
<td>28M 22F

<table>
<tr><td></td><td>Group A</td><td>Group B</td><td>Group C</td><td>Group D</td></tr>
<tr><td>Male</td><td>3</td><td>5</td><td>11</td><td>9</td></tr>
<tr><td>Female</td><td>2</td><td>3</td><td>7</td><td>10</td></tr>
<tr><td>Pneumonitis Present</td><td>2/5</td><td>4/8</td><td>6/18</td><td>8/19</td></tr>
<tr><td>CVS anomaly</td><td>1</td><td>1</td><td>3</td><td>2</td></tr>
<tr><td>GI Anomaly</td><td>0</td><td>1</td><td>2</td><td>1</td></tr>
<tr><td>Total Anomaly</td><td>2/5
40%</td><td>3/8
37.5%</td><td>6/18
33%</td><td>6/19
31%</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
</table>

All 4 groups were comparable for age at presentation (58hrs (10hrs-9days), BW (average BW 2150G (1100-3100), pneumonitis and associated anomalies

Overall anastomotic leak 15/50 (30%)

<table>
<tr><td>Gap Length</td><td>N</td><td>Anastomotic Leak</td></tr>
<tr><td>Group A</td><td>5</td><td>4 (80%)</td></tr>
<tr><td>Group B</td><td>8</td><td>4 (50%)</td></tr>
<tr><td>Group C</td><td>18</td><td>5 (28%)</td></tr>
<tr><td>Group D</td><td>19</td><td>2 (10.5%)</td></tr>
<tr><td>Total</td><td>50</td><td>15 (30%)</td></tr>
</table>

<table>
<tr><td>Groups</td><td>Odds Ration</td></tr>
<tr><td>D</td><td>1</td></tr>
<tr><td>C</td><td>3.27</td></tr>
<tr><td>B</td><td>8.5</td></tr>
<tr><td>A</td><td>34</td></tr>
</table>
P=0.002

Overall Anastomotic Stricture 10/35 (29%)

<table>
<tr><td>Gap Length</td><td>N</td><td>Mortality</td><td>Anastomotic Stricture</td></tr>
<tr><td>Group A</td><td>5</td><td>4 (80%)</td><td>1 (100%)</td></tr>
<tr><td>Group B</td><td>8</td><td>4 (50%)</td><td>3 (75%)</td></tr>
<tr><td>Group C</td><td>18</td><td>4 (22%)</td><td>3 (22.5%)</td></tr>
<tr><td>Group D</td><td>19</td><td>3 (15.6%)</td><td>3 (19%)</td></tr>
<tr><td>Total</td><td>50</td><td>15 (30%)</td><td>10 (29%)</td></tr>
</table>
</td>
<td>Gap length used to predict prognosis

Gap length can predict the chances of anastomotic leak, with highest incidence being in cases of long gap EA as the anastomotic site is under tension and there is excessive mobilization of both pouches prior to anastomosis

There was significant difference in the incidence of anastomotic leak between the groups

There was an increased incidence of stricture in the groups with long gap as anastomotic tension and leak in patients with long gap can result in stricture. Hence gap length can predict chances of stricture after primary EA repair and hence long term outcome. However in this study these values were not statistically significant.

GER can also cause esophageal stricture but was not measured in this study

Anastomotic leak resulting in septicemia accounted for 53% of total mortality. Mortality was higher in those with long gap. Hence mortality can be predicted by measuring gap length

Gap length can predict short term and long term complications in EA patients</td>
</tr>
</table>

			Overall Mortality 15/50 (30%) Groups / Odds Ration D / 1 C / 1.5 B / 5.33 A / 21.33 P=0.0025 Of 15 mortalities 8 died due to septicemia following anastomotic leak. All mortalities in Group A were due to anastomotic leak where as none in Group D were due to septicemia	

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	GER	Results on Stricture Dilatation	Conclusion
Hoffer et al (5) 1987	Retrospective Review 1983-1986	9 EA patient Mean age 5years(6wks-17yrs) 7 Primary anastomosis 1 gastric interposition 1 colonic interposition Balloon Dilatation Diameter of first balloon (B) was usually chosen to be equal to the diameter of the distal esophagus (E) (B/E=1) If uninflated balloon did not pass through the stricture a smaller balloon was used Balloon catheters >20mm tolerated only 1.5ATMs Usually 2 dilatation/setting each lasting 3 minutes Size of distal esophagus was calculated from contrast studies corrected for magnification Response time was defined as the time between a dilatation and a successive dilatation, another procedure or the end of the study Balloon dilatation done in patients with colonic and gastric interposition as tortuous anastomotic strictures made strictures inaccessible to bouginage	GER suspected on Barium in 5 GER proved by pH Metry in 3 (pH <4 >4min in 24 hours) Esophageal motility abnormal in 2 Endoscopy in 4 and showed esophagitis on histology in ¾ 3 patients with esophagitis: 1 stricture at anastomosis 1 stricture at anastomosis + distal 1 distal stricture only All 3 with esophagitis treated with antacids or cimetidine prior to dilatation 2 had Nissen fundoplication prior to dilatation but continued to have GER	9 patients had 26 dilatations 1-8/patient 7 patients with primary anastomosis were treated with 15 balloon dilatations The diameter of the distal esophagus ranged from 10-30mm B/E >/= 1 in 6/7 for 12 dilatations The 3 dilatations with B/E <1 had 6 months or less of response Only 2 strictures extended beyond anastomosis. Length of stricture had no bearing on results The initial B/E Ratio ranged from 0.6-1.1 in 7 patients Response/Dilatation 0-18months Second B/E ratio 1-1.5 in 5 patients Response/dilatation 2-24 months Third B/E ratio1.3 in 2 patients Response/dilatation1-14months 4 Asymptomatic at 13-23 month follow up 3 Symptomatic: 1 recurrence due to stopping anti reflux medications and home bouginage 1 patient with GER developed perforation post dilatation and requires further bouginage	Balloon dilatation is superior to bouginage because only axial forces are applied to stricture increasing effectiveness of dilatation and reducing risk of perforation. Balloons can be expanded to larger size and are not limited by size of pharynx unlike a bougie Balloon can be distended to size of distal esophagus which is not achievable with bouginage Signs of maximal esophageal distension are similar in both techniques. In bouginage progressive resistance to passage suggests endpoint reached. In Balloon inability to reduce the waist any further suggest maximum effectiveness of treatment has been reached Patient who had perforation probably had excessive increase in size of balloon (x3 incremental sizes in 1 sitting). This patient also not treated for suspected reflux esophagitis which may have contributed to severity of stricture, lack of improvement between dilatations and tendency to rupture with aggressive dilatations Normal esophagus could be stretched 1.6-2 times its resting diameter without perforation. Esophageal mucosa is responsible for tensile strength of esophagus (rather than muscular layer) only when esophagus is dilated to near its failure diameter (3 times resting diameter). This could be why reflux esophagitis predisposes to esophageal rupture during dilatation Persistent or late strictures could be due to GER If GER is suspected important to investigate with scintigraphy, pH Metry and endoscopy and treat effectively

					Peptic esophageal stricture should be treated with reflux treatment in addition balloon dilatation or surgical bouginage combining with home bouginage in severe cases Treatment of reflux esophagitis in persistent or recurrent strictures may enhance the safety and effectiveness of balloon dilatation or bouginage procedure

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Stratification of results of early and late complications following EA repair based on gap length	Conclusion
Brown et al (6) 1996	Retrospective Review 1977-1993	66 EA patients 41M 25F **Gap Length** Long Gap >3cms Intermediate Gap >1cm but </= 3cm Short Gap </= 1cm **Long Gap** Mean BW 2183g (1200-2929) Gestation 34 (29-41) Associated anomaly Cardiac 8 (50%) GIT 1 (6%) Tracheal 3 (19%) Vertebral 1 (6%) Urinary tract 1 (6%) EA Types Type A 4 (25%) Type C 11 (69%) Type D 1 (6%) **Intermediate Gap** Mean BW 2615g (1200-3400) Gestation 35 (30-42) Associated anomaly Cardiac 4 (25%) GIT 2 (12%) Tracheal 6 (38%) Vertebral 2 (12%) Urinary tract 1 (6%) EA Types Type A 1 (6%) Type C 14 (88%) Type D 1 (6%) **Short Gap** Mean BW 2846g (1200-4340) Gestation 39 (29-42) Associated anomaly Cardiac 11 (32%) GIT 3 (9%) Tracheal 4 (12%) Vertebral 3 (9%) Urinary tract 2 (6%) EA Types Type A 0 (0%) Type C 32 (94%) Type D 2 (6%)	**Early Complications** **Long Gap** Chest Infection 31% Pneumothorax 37% Anastomotic Leak 31% Stricture 44% Total Anastomotic Complications 69% **Intermediate Gap** Chest Infection 25% Pneumothorax 43% Anastomotic Leak 25% Stricture 31% Total Anastomotic Complications 50% **Short Gap** Chest Infection 17% Pneumothorax 30% Anastomotic Leak 6% Stricture 17% Total Anastomotic Complications 21% Direct correlation between mean length of hospital stay and gap categories, p <.05 6 deaths. 3/6 in long gap group 2 due to recurrent TEF In early complication parameters including chest infection, pneumothorax, anastomotic leak and stricture the babies with short gap fared best The incidence of anastomotic complications was highest in the long gap and intermediate in the intermediate gap group, p<.05 Significant difference in occurrence of anastomotic leak between long and short gap patients (p=.04) and total anastomotic complications between long and short gap patients (p=.002) No significant difference between long and short gap patients for chest infection, pneumothorax stricture (although there was a higher incidence of stricture in long gap) No significant difference between intermediate and short gap patients for chest infection, pneumothorax, anastomotic leak stricture (although there was a higher incidence of stricture in intermediate gap)	Classification of patients based on gap length divides patient population more evenly (long 24%, intermediate 24%, short 52%) in comparison to Spitz (Group I 79%, Group II 19%, Group III 2%) Complications related to anastomosis (leak and stricture) are more frequent greater the gap length Other complications are less relevant to gap length Short gap patients spend less time in hospital and more likely to achieve normal growth. This data is useful to parents (expectations, QOL) and health planners. This data can be used to evaluate efficacy of treatment strategies. This classification better than Hands one which would have overestimated morbidity on long gap group and under estimated it in other groups Spitz classification identified 2 deaths in patients with LBW and cardiac anomaly, but these patients also had long gap In Spitz best prognostic group out of 2 deaths 1 had long gap. Hence gap length should not be used as sole criteria for predicting mortality Main value of gap length is its predictive value on long term outcome including failure to thrive Gap length measurement can thus be used to predict short and long term complications I EA patients

			Late Complications **Long Gap** Chest Infection 44% Stricture 75% Incoordination 25% GER 56% Recurrent TEF 6% FTT 56% Total major complications 100% **Intermediate Gap** Chest Infection 37% Stricture 50% Incoordination 25% GER 37% Recurrent TEF 6% FTT 43% Total major complications 75% **Short Gap** Chest Infection 42% Stricture 60% Incoordination 39% GER 36% Recurrent TEF 6% FTT 18% Total major complications 68% Number of subsequent admissions with late complications was significantly higher in long gap group There was a significant difference between incidence of failure to thrive (FTT) (p=.01) and total major complications) (p=.03) between long gap and short gap but none of the other variables were significant There was also no significant difference in the occurrence of any of the late complication variables between intermediate gap and short gap patients For patients followed up for <2yrs 60% with short gap achieved normal growth compared to 33% in other groups. For those followed up for >2yrs 91% of short gap achieved normal growth compared with 83% in intermediate gap and 57% in long gap **Requirement for further surgery** **Long Gap** Stricture resection 12% Nissen Fundoplication 25% Repair of recurrent TEF 6% Total 50%	

			Intermediate Gap Stricture resection 12% Nissen Fundoplication 31% Repair of recurrent TEF 6% Total 50% **Short Gap** Stricture resection 3% Nissen Fundoplication 3% Repair of recurrent TEF 6% Total 12% Long gap patients had significantly more fundoplication (p=.054) and total further surgery (p=.029)than short gap patients Intermediate gap patients had significantly more fundoplication(p=.016) and total further surgery (p=.029)than short gap patients	

STRICTURE in EA-TEF

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of Patients
Patient Characteristics</th><th>Results of Indwelling Esophageal Balloon catheter for esophageal stricture</th><th>Conclusion</th></tr>
<tr>
<td>Van Der Zee et al (7)
2013</td>
<td>Retrospective Review
2004-2012</td>
<td>19 Patients
7 EA patients
7 Caustic burns
2 GER
3 Unknown cause

7 EA
5 Long Gap
2 Type C EA
Age 4weeks-2years</td>
<td>2 Types of indwelling catheters used:
Olympus Endo Therapy Esophageal Balloon Dilator BE2, size 4cm/6mm, 4cm/8mm, 4cm/10mm
Boston Scientific Ultra Thin SDS Standard, size 4cm/6mm, 4cm/8mm, 4cm/10mm, 8cm/10mm

Catheter position checked by external markings by parent prior to insufflation with 15-20cc of air. Insufflation done for 3s then desufflated. Done 3 times a day. Patients able to drink and eat solid food with catheter in situ. Guide wire channel can be used for drip feeds.

EA Patients

<table>
<tr><th></th><th>Long Gap</th><th>Type C EA</th></tr>
<tr><td>Age (months)</td><td>1-24</td><td>1-2</td></tr>
<tr><td>Endoscopies With Indwelling catheter</td><td>2-4</td><td>1</td></tr>
<tr><td>Total endoscopies</td><td>2-16</td><td>1-6</td></tr>
<tr><td>Number of Balloon episodes</td><td>1-2</td><td>1</td></tr>
<tr><td>Duration of Treatment (months)</td><td>1-12</td><td>7-24</td></tr>
<tr><td>Duration of Indwelling Balloon (months)</td><td>1-5</td><td>2.5</td></tr>
<tr><td>Rethoracotomy Rethoracoscoy</td><td>0</td><td>0</td></tr>
<tr><td>Complications</td><td></td><td></td></tr>
<tr><td>Restenosis</td><td>3</td><td>1</td></tr>
<tr><td>Dislodgement</td><td>0</td><td>0</td></tr>
<tr><td>Balloon leakage</td><td>0</td><td>1</td></tr>
<tr><td>Sputum retention</td><td>0</td><td>1</td></tr>
<tr><td>Mortality</td><td>0</td><td>0</td></tr>
</table>

1 of the restenosis was in LGEA with jejunal interposition at distal anastomosis

Sputum retention occurred in 4wk old due to which catheter was removed and patient required 5 more dilatations

6/7 had fundoplication, except patient with jejunal interposition</td>
<td>Daily indwelling balloon dilatation catheter can be used in EA patients with persistent symptoms due stricture despite repeated dilatations

The principle is to keep the esophagus open at its optimal diameter after endoscopic dilatation has already taken place

These patients can feed/eat which can be a problem with esophageal stents. It is well tolerated

No GA/sedation or hospital admission required

Reduces total number of endoscopies during treatment

Helps avoid reconstructive surgery

Dislodgement and balloon leakage can occur, but they tend to occur more in patients with stricture due to caustic burns

Indwelling balloon catheter is safe to use by parents at home. It does not dislodge frequently. It reduces need for endoscopies during treatment and need for re thoracotomy/scopy or esophageal replacement. It helps maintain the lumen of the esophagus at its desired diameter</td>
</tr>
</table>

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Results on EA patients with Congenital Esophageal Stenosis (CES)	Conclusion
Ibrahim et al (8) 2007	Prospective case cohort study 1996-2004	57 consecutive EA repairs 4 Type A EA 53 Type C EA All had histological studies of surgical specimens obtained from tip of lower esophageal pouch (LEP) Patients with histological picture consistent with CES (Fibromuscular disease (FMD) or tracheobronchial remnants (TBR) with or without cartilage in presence of stratified columnar epithelium and sero mucous glands were included **8/57 (14%) had histologic picture suggestive of CES** 2 FMD 4 TBR without cartilage 2 TBR with cartilage 6/8 were females GA mean 34.6wks (30-37) BW mean 2 kg (1.3-2.9) 6 Type C EA 2 Type A EA Case with pure EA with gastric pull up was excluded from further study All had initial Barium swallow at 7-10 days post repair Those with recurrent respiratory problems, dysphagia and FTT were restudied with contrast study, endoscopy. **Dysmotility in contrast study**: **Minor**-aperistalsis, antiperistalsis, simultaneous or uncoordinated contractions **Major**- Transit time for bolus to reach stomach was >5 minutes Follow up mean 5years (3-8) Cases classified according to histology Group I 2 with FMD Group II 4 with TBR without cartilage GROUP III 2 TBR with cartilage	23/57had strictures 6/23 had CES Stricture at anastomotic site extending distally 2 FMD and 1 TBR with cartilage Stricture only at anastomotic site in 3 of TBR without cartilage Onset of symptoms mean 3.4months (2-10) Time lag between onset of symptoms and definitive treatment with resection in 2 cases (6$7 months) Symptoms: Respiratory including aspiration Dysphagia Failure to thrive (FTT) in 4/8 **Initial Barium** Normal motility 3 Minor dysmotility 4 Slight anastomotic stricture 5 Moderate GER all **Later Barium showed Triad of:** Dysmotility (minor 5, major 2) Stricture in 6 GER all **All had significant GER** **Endoscopy** Normal mucosa 4 Second degree esophagitis 2 Scope could not pass through 1 **Fundoplication 4** No benefit seen in 2 patients with major dysmotility **Treatment** **4 TBR without cartilage:** Dilatation and medical anti reflux measures was successful in 3 with TBR without cartilage 1 case pure EA with TBR without cartilage did not have stricture but needed Thal fundoplication **2 TBR with cartilage** 1 with TBR with cartilage required resection of anastomotic site with frequent dilatations 1 case of TBR with pure atresia involving whole lower pouch to distal esophagus required resection with gastric pull up	CES seen in 14% of EA in this study Incidence in pure EA (50%) was higher than in Type C (11.3%) EA. This should be considered while doing delayed repair in pure EA CES due to TBR (75%) was commoner than due to FMD (25%) CES may involve anastomotic area or even extend distally to variable distance. Distal separate area of CES can also be present CES should be suspected when there is clinical triad of recurrent aspiration, dysphagia and FTT. Initial investigation should be esophagogram All CES in this series had significant GER. Endoscopy and biopsy, pH metry and manometry may be required to distinguish GER from CES and even them may be difficult Without preliminary histology difficult to distinguish between TBR and FMD. Endoscopic biopsy may not show deep seated tissue. Endoscopic ultrasound may be useful Anti reflux treatment with balloon dilatation should be initial treatment for CES with EA as in all cases of TBR with cartilage this was successful in this series Cases of TBR with cartilage will require limited resection and primary anastomosis if balloon dilatation fails on 3 occasions. Surgery is also indicated if sufficient dilatation is not achieved or if symptoms recur soon after dilatation. Resection without prior dilation could be considered with preoperative knowledge of histologic picture. Fundoplication is recommended after resection if it disturbs the GE junction Cases with FMD usually respond to dilatations. Some may require myotomy with Nissens failing which a limited resection may be required TBR without cartilage may not cause stricture. If stricture develops it response well to dilatations without radiological improvement.

			2 FMD 1 case of FMD did not improve after dilatations, myotomy, Nissen fundoplication and became dependent on gastrostomy and required resection 1 case of FMD had frequent dilatations and Nissen fundoplication and esophageal diverticulectomy and only improved on 4 dilatations post diverticulectomy	Unlike isolated CES GER is common In the presence of triad od stricture, GER and dysmotility anti reflux surgery should be avoided before definite surgery for the stricture and if needed a partial wrap with a gastrostomy is recommended CES should be considered in etiology of anastomotic stricture. Its extent should be determined by using frozen section biopsy. This is the first study looking at long term follow up of CES in EA patients Authors recommend taking surgical specimen routinely for histopathologic studies from tip of LEP during primary repair of EA.

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Results of antegrade dilatation via gastrostomy and steroid injection into stricture	Conclusion
Gandhi et al (9) 1989	Prospective case cohort study 1975-1989	12 patients with severe esophageal stricture Mean age 26months (4mths-5yrs) at time of symptom onset 7M 5F **2 Groups** **Group 1** Caustic ingestion 6 patients **Group 2** **5 EA patients** 1 of unknown etiology (probable acid peptic irritation of iatrogenic perforation of cervical esophagus) All had failed previous esophageal dilatation attempts **Definition of severe esophageal stricture:** Significant luminal narrowing Complete intolerance of solids associated with episodes of choking severe enough to cause profound respiratory embarrassment Progressive FTT and/or Total obstruction as manifested by intolerance of liquids as well as solids Average stricture length 3.5cms (1-10)	**Treatment** Esophagoscopy Stamm Gastrostomy If GER present on fluoroscopy Nissen Fundoplication Esophagoscopy with endoscopically guided 4 quadrant intra lesional steroid (Triamcinolone acetate 1%, 0.1ml) Mean of 4.3 steroid injections (1-8) needed Antegrade string guided esophageal dilatation under GA at weekly intervals until complete resolution of stricture was obtained Diameter of esophagus during dilatation was never increased by more than 4Fr at 1 setting **Results of treatment of Group 1 shown in Table1** Average length of stricture 5.4cms Mean of 5.2 injections of steroid 1 patient had 2 strictures (proximal resolved but distal needed resection **Results of treatment of Group 2 shown in Table2** With 1 exception average stricture length 1.2cms Mean of 2 injections to achieve complete resolution of symptoms **Complications:** Single group 1 patient who had perforation which responded to antibiotics All patients remain symptom free Mean follow up 6.2yrs (1-11)	String guided esophageal dilatation when coupled with endoscopically guided steroid injection is a safe and reliable method for treatment of severe esophageal strictures. Complete resolution of symptoms was achieved in all patients who received full course of treatment By this method need for resection or esophageal replacement is obviated with preservation of a functional native esophagus However conservative management mandates the need for long term surveillance for adenocarcinoma of the esophagus

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Results of prophylactic treatment with PPI on incidence of strictures	Conclusion
Hagander et al (10) 2012	Retrospective Review 2001-2009	32 EA patients received prophylactic PPI during 2001-2009 Historical control of 63 EA patients did not receive PPI between 1983-1995 3 patients who did not receive PPI from study period were added to control group Contrast study done at 4weeks post repair and in presence of feeding difficulty For suspected stricture a calibration was performed. If narrowing was seen during balloon inflation the procedure was defined as dilatation Endoscopic balloon dilatation done for strictures **PPI** Omeprazole/esomeprazole 2mg/Kg once a day from day 3 till 3 months of age and during period of dilatations Follow up was set at 1 yr after last dilatation No one had pH-impedance or esophageal biopsies taken	The study (PPI) and the control groups were comparable regarding patient characteristics, gestational age, BW, prevalence of chromosomal abnormality and VACTERL malformations. Survival rate and prevalence of surgery was similar in both groups **(Table 1)** Occurrence of anastomotic leakage was significantly different between both groups **(Table 1)** Data on number of dilatations, age at first and last dilatation are shown in **Table 2**. Dilatation frequency needed in each child did not differ significantly between the groups Approximately 50% of children required dilatations. Number of dilatations varied between (1-21) with a median of 3 and 4 in PPI and control group No stricture resection done in PPI group Children in PPI group were significantly younger at time of dilatation No one in PPI group had fundoplication as their GER could be treated by medication	Prevalence of stricture did not differ significantly between PPI (56%) and control (42%) groups Hence hypothesis that prophylactic PPI prevents anastomotic stricture formation could not be supported Complication following dilatation occurred more frequently in the control group. This could due to use of PPI in the study group, technical advancement, Perforations in control group were treated conservatively. Lack of perforation in PPI group could be due to change in dilatation practice Majority of patients in PPI group presented with signs of esophageal obstruction (81%). 19% were asymptomatic. In patients with no verified stricture obstructive symptoms were seen in 50%. This could be due to dysmotility, GER or tracheomalacia Long gap atresia was seen in both groups (6% in PPI group and 13% in control group), and no significant difference was seen. There was no correlation between duration of PPI treatment and time of appearance of stricture. The mean time on PPI (43 days longer in patients who did not develop strictures compared to those who developed strictures (p=NS). This suggests that 3 months on PPI might be too short to prevent stricture formation Number of dilatations needed was equivalent in both groups Strictures were detected earlier in PPI group and age of last dilatation was lower. This could be due to tendency for earlier intervention in PPI group. Strictures being detected and treated earlier prevented serious complications in PPI group Study limitation was use of historical control and lack of randomization Even though PPI use did not reduce incidence of strictures they are of value in treatment of GER

Table 1 Patient Characteristics Documented in the Study (PPI) Group and the Control Group

	Study Group 2001–2009 $n = 32$	Control Group 1983–1995 $n = 66$[a]
Gender: male/female	66%/34%	55%/45%
Gestational age		
Weeks $\geq$ 37 Premature weeks $<$ 37	56% 44%	52% 48%
Birth weight		
$<$ 1500 g 1500–2500 g $>$ 2500 g	1 (3%) 9 (28%) 22 (69%)	5 (8%) 26 (39%) 35 (53%)
Type of atresia; Type A/Type C	6%/94%	13%/72%
Associated malformations Chromosomal Vertebral Anorectal Cardiac Trachea Oesophageal Renal Limb	$n = 32$ 3% 13% 3% 25% 94% 100% 9% 13%	$n = 63$ 5% 3% 4% 14% 71% 100% 6% 3%
Underwent surgery	95% ($n = 42$)	86% ($n = 66$)
Anastomotic leakage	13% ($n = 4$)	15% ($n = 10$)
Survival	88% (37/42)	87%

[a]63 from the control group and 3 children operated during the study period 2001 to 2008 who did not receive PPI.

Table 2 Numbers of Dilatations Performed in the PPI and the Control Groups, Respectively. Minimum, Maximum, and Mean Ages at First and Last Dilatation in Patients with Stricture Formation are Presented in Days. $p < 0.05$ was Considered Statistically Significant

Treated with PPI	Yes	No	Statistics *p* value
Number of children	32	66	
Number who needed dilatation	18 (56%)	28 (42%)	0.283[a]
Number of dilatations needed			
Median (range)	3 (1–21)	4 (1–20)	0.520[b]
Age at first dilatation			
Days: median (range)	63 (28–346)	210 (15–1159)	0.011[b]
Age at last dilatation			
Days: median (range)	138 (28–1959)	420 (61–1586)	0.005[b]
Perforation during dilatation	0%	18%	0.017[a]

[a]Fisher's exact test.
[b]Mann-Whitney *U* test.

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Suture Material	GER	Anastomotic Leak	Tracheomalacia Recurrent TEF	Operator Experience	Stricture Symptoms Dilatation of strictures	Conclusion
Chittmittrapap et al (11) 1990	Retrospective review 1980-1987	199 EA patients 15 excluded 74 patients in stricture group 102 patients showed no stricture 8 in questionable group Patients who had swallowing difficulties (dysphagia, vomiting, poor feeding) or recurrent episodes of respiratory infection or foreign body including food bolus impaction in whom a stricture that required dilatation was demonstrated endoscopically were included in the "Stricture" group Patients who had symptoms especially food bolus obstruction but had normal esophageal lumen and did not require dilatation were classified in the "questionable" group Follow up 4months-7years	Effect of suture materials used for anastomosis on the subsequent development of anastomotic stricture without regression for GER is shown in **Table 1** There was a significant increase in stricture rate when silk was used, p<.05 with and without regression of the reflux factor. Relative risk was 1.72 and 1.49 compared with polyglycolic acid and polypropylene sutures No significant difference between polyglycolic acid and polypropylene sutures seen.	**Table 2** shows effect of GER on development of subsequent anastomotic strictures GER significantly increased the stricture rate, p<.01 both with and without regression of the silk suture factor. The relative risk of GER was 2.29 Incidence of GER and requirement for fundoplication increased in proportion to number of dilatations required, **Table 8** 39/74 had GER 19/39 had Nissen fundoplication 18/19 developed stricture symptoms within 6 months post repair	Anastomotic leak significantly affected stricture rate, p<.05., shown in **Table 3** The relative risk was 2.04	Stricture rate was unaffected by tracheomalacia , **Table 4** Stricture rate was unaffected by recurrent TEF, **Table 5** 5 developed concurrent strictures and recurrent TEF	Stricture rate was unrelated to status of surgeon, **Table 6**	Symptoms: Swallowing difficulties/poor feeding 79.7% Food bolus impaction in 6 all >1yr All responded to 1-2 dilatations Age of onset of first symptom shown in **Table 7** Earlier the onset more dilatations were required All patients requiring >5 dilatations or resection developed symptoms within 6 months post repair Dilatation was successful in 71/74 21 (28.4%) had 1 21 (28.4%) had 2 7 (9.5%) had 3 8 (10.8%) had 4 14 (18.9%) needed 5 or more 3 developed perforation post dilatation No prophylactic dilatations done 2 needed resection when dilatation did not work Gastric interposition in 1 with stricture + recurrent TEF	Significant predisposing factors for development of anastomotic stricture included use of braided silk suture, GER and anastomotic leak Tracheomalacia, personnel factors and recurrent TEF did not affect rate of stricture formation 95% of strictures responded to dilatation alone All patients requiring stricture resection or esophageal substitution and those requiring >5 dilatations developed symptoms within 6 months after EA repair Fundoplication done in 25.7% of EA patients with strictures

Table 1. Suture Materials Used for Repair and Incidence of Stricture

	Stricture	No Stricture	Questionable	Not Evaluated	Total
Silk	15	12	1	2	30
Polyglycolic acid	22	46	3	7	78
Polypropylene	33	36	3	5	77
Ethibond	3	7	1	1	12
No data of suture	1	1	0	0	2
Total	74	102	8	15	199

Table 2. The Presence of Gastroesophageal Reflux (GER) and Stricture Formation

	Stricture	No Stricture	Questionable	Not Evaluated	Total
GER	39*	22†	4	0	65
No GER	30	80	4	3	117
Not evaluated	5	0	0	12	17
Total	74	102	8	15	199

* 19 required Nissen's fundoplication.

† 15 required Nissen's fundoplication.

Table 3. Anastomotic Leakage Correlated to Stricture

	Stricture	No Stricture	Questionable	Not Evaluated	Total
Leak	20	7	0	7	34
No leak	54	95	8	3	160
Not evaluated	0	0	0	5	5
Total	74	102	8	15	199

Table 4. Tracheomalacia and Stricture

	Stricture	No Stricture	Questionable
Tracheomalacia	23*	18†	1
No tracheomalacia	51	75	7

NOTE. Only 175 of 184 were evaluated for tracheomalacia.

*16 required aortopexy.

†14 required aortopexy.

Table 5. Recurrent Tracheoesophageal (TE) Fistula and Stricture Formation

	Stricture	No Stricture	Questionable
Recurrent TE fistula	5	10	0
No recurrent fistula	69	92	8

Table 6. Personnel Factor and Stricture

	Stricture	No Stricture	Questionable
Operated by consultants	42	60	4
Operated by trainees	30	42	4

NOTE. There is no record on the personnel factor in two of 184 cases.

Table 7. The Presenting Symptoms of the First Attack Related to Type of Treatment

No. of Dilations Required	Symptoms or Problems			Onset (months)	
	Swallowing	Respiration	Food Obstruction	0-6	>6
1	15	2	4	10	11
2	16	3	2	15	6
3	7	0	0	5	2
4	8	0	0	5	3
>5	10	4	0	14	0
Resection/substitution	3	0	0	3	0
Total	59	9	6	52	22

Table 8. Gastroesophageal Reflux and Antireflux Operation in the Stricture Group

No. of Dilations Required	No. of Cases	Presence of Reflux	No. Nissen Performed
1	21	4	3
2	21	12	6
3	7	6	2
4	8	4	1
>5	14	11	7
Resection/ substitution	3	2	0
Total	74	39	19*

*Onset less than 6 months, 18 cases; onset greater than 6 months, one case.

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Results on use of Dynamic Esophageal Stents for Strictures	Conclusion
Caldaro et al (12) 2013	Retrospective Review 1992-2012	387 EA patients with esophageal strictures Mean age 38.6months (3-125) 1583 Savary dilatations done Mean 4/patient (1-24) 26 (6.7%) of 387 patients needed esophageal stenting due to recurrent stricture despite 5endoscopic dilatations All patients got dexamethasone 2mg/kg/day for 3 days after placement of dynamic stent Stent left in place for 40 days PPI (omeprazole or lanssoprazole 1-2mg/kg/day given while stent is in situ Contrast study done to exclude leakage and feeding with soft diet commenced Post treatment stent removed under GA and endoscopy done to assess anastomosis 1 month later barium swallow done to assess stability of esophageal caliber and motility of esophageal wall Treatment considered effective if patient is able to eat solid food without dysphagia and xray shows resolution of stricture In follow up GERD investigated with endoscopy and biopsy and pH Metry	No intra operative complications All patients able to resume normal diet 2 major complications of subclavian esophageal fistula due to unknown aberrant right subclavian artery (ARSA) 4 minor complications 2 stent displacement 2 laryngitis Stent was effective with complete resolution of stricture in 21/26 (80.7%) Mean follow up 5.4yrs (6months-20yrs) 5/26 (19.2%) stricture relapse and surgical resection with jejunal interposition in 1 and resection and reanastomosis in 4 Nissen fundoplication done for Severe GERD in 15/26 (71.4%) 2 (9.5%) had dysphagia due to dysmotility despite normal esophageal diameter and needed gastrostomy feeds	Custom dynamic stent (DS) is an effective option for recurrent post surgical strictures that do not respond to initial endoscopic dilatations Results are durable in long term follow up Experienced endoscopic team essential for best results Advantages of DS include the fact that it is custom built according to length and diameter of stenosis making displacement rare It favors esophageal motility during passage of food between stent and esophageal wall In addition to normal diet the naso gastric tube incorporated in the stent could be used for feeds in patients with initial severe dysphagia DS was well tolerated Complete stricture resolution in 80%. In the remaining 4/5 patients the stricture was shorter after DS and amenable to stricture resection and re-anastomosis 2 major complications due to ARSA and now preoperative imaging to exclude vascular anomalies in EA patients done prior to DS GERD plays a role in recurrent strictures and fundoplication must be considered to avoid relapse of stricture. In this study majority of patients needed fundoplication after initial period of treatment with PPI

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Stricture	Conclusion
Peyvasteh et al (13) 2006	Retrospective Review 1999-2000	74 EA patients 21 died 2 with Type A EA were excluded 51 Type C EA patients included in study Mean gestational age 37.1wks (35-39) **2 Groups** **Group A developed stricture** **Group B had no stricture**	**Group A (with stricture)** 26 16M 10F Anastomotic Leak 10 GER 17 Type of anastomosis End to End 24 End to Side 2 Suture Silk 3 Vicryl 23 Type of thoracotomy Extra pleural 24 Intra pleural 2 Technique of anastomosis One layer 19 2 layers 17 **Group B (without stricture)** 25 12M 13F Anastomotic Leak 0 GER 5 Type of anastomosis End to End 21 End to Side 4 Suture Silk 1 Vicryl 24 Type of thoracotomy Extra pleural 21 Intra pleural 4 Technique of anastomosis One layer 17 2 layers 18 38.46$ developed anastomotic leak in Group A vs 0 in Group B , p=.001 65.4% had GER in Group A vs 20% in Group B, p=.001	All patients with anastomotic leak developed stricture. Anastomotic leak and GER have major role in stricture development in EA patients, so treatment and prevention of these complications is important The risk of stricture formation is a potential threat for up to 1 year in patients without GER and up to 18 months in patients with GER

			No significant differences between groups for type of thoracotomy, anastomotic technique and type of suture used 57.7% (15) of patients who developed strictures presented between 0-6months, 34.9% (9) between 6-12 months 7.7% (2) between 12-18 months No new strictures after 18 months Strictures resolved after 1-3 dilatations in 11 (42.3%) 9 (34.6%) needed resection Fundoplication done in 6 (23.1%) for failure of medical treatment and non responding GER No significant difference in time to develop stricture in patients with and without GER	

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Results of high dose IV Methylprednisolone for Treatment of esophageal stricture	Conclusion
Morikawa et al (14) 2008	Case Series	2 patients Case 1 EA Patient Long Gap Type B EA Delayed Repair at 10 months Anastomotic Leak 3cm Stricture Balloon dilatations every 2-3 weeks Fundoplication for GER at 15 months This had no effect on stricture Intra lesional steroid injection (2mg Dexamethasone into each quadrant) following balloon dilatation from age 3 years was partially effective CT scan showed thickened wall at stricture site Magnet therapy resulted in worsening of stricture due to slippage of magnets Case 2 Corrosive stricture	Balloon dilatation of stricture with intra lesional steroid injection (2mg Dexamethasone into each quadrant) Followed by High dose intravenous methyl prednisolone at dose of 25, 15, 10, 5, 2mg/Kg for 4 days each Cimetidine and Ampicillin also given for 1 week This was followed by oral prednisolone daily 2, 1, 0.5mg/Kg for 1 week each as outpatient Resulted in resolution of stricture without significant complication. Moon face improved with withdrawal of oral prednisolone EA Patient and corrosive stricture patient are now tolerating all types of food for 8 and 7 months respectively	High dose intravenous methylprednisolone in addition to intra lesional injection of dexamethasone following balloon dilatation is an effective strategy for persistent esophageal strictures Systemic administration of steroids is able to deliver the medication to the stenotic lesions better than endoscopic injection because often the fibrotic stricture makes it difficult o inject the steroids effectively Steroids given post dilatation also suppresses the initial inflammation which occurs in the first 3 days of wound healing Short course of high dose steroids did not result in any major systemic complication Regular ongoing surveillance is needed as there is risk of carcinoma developing in damaged esophagus

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Results of management of Congenital Esophageal Stenosis (CES)	Conclusion
Vasudevan et al (15) 2002	Retrospective Review 1980-1999	123 EA Patients 6/123 (4.9%) had CES All females Gestational Age 32-42 weeks BW1150-3120g 2 Type C EA 1 Type E EA 1 Type A EA (this patient also had duodenal atresia and duodenal web) 2 had isolated CES Diagnosis By contrast study postnatally in 5 1 by prenatal ultrasound Symptoms Early Feed Intolerance in 2 3 had delayed onset of symptoms Location Apart from 1 all located in distal esophagus	4/7 stenosis treated by surgical resection 3 treated by esophageal dilatation Complications 2 developed perforations post attempted dilatation Histopathology of resected specimens Tracheobronchial remnants in 3 Submucosal thickening (Fibromuscular) in 1	Isolated CES is rare 2/123 (1.6%) CES associated with EA has a higher incidence (4/123 (3.25%) Patients with CES should be treated first with dilatation. Dilatation can be complicated by perforation If ineffective, resection is required Resection is not always curative as post resection strictures can develop as in 2 patients in this series **Table 3** shows results of other series of CES as well as this study. The best treatment for a tracheobronchial remnant type of CES is with surgical resection 3/7 stenosis (42.9%) were treated solely with esophageal dilatation. The lesions treated effectively with dilatation are usually fibromuscular CES are usually diagnosed soon after birth. Patients have symptoms of dysphagia and food/foreign body trapping They show no endoscopic evidence of reflux esophagitis and there is no radiographic evidence of external stricture. Fibromuscular thickening is a diagnosis of exclusion

Table 3. Comparison of Recent CES Series

CES Study	No. of Patients	Method of Treatment	Histopathology*
Nishina et al (1981)[3]	2	Surg res (2/2)	Trach-br rem (2/2)
Nihoul-Fékété et al (1987)[2]	20	Esoph dil (9/20)†; surg res (11/20)	Trach-br rem (4/20); mem diaph (6/20); fib-mus thick (1/20)
Neilson et al (1991)[4]	6	Esoph dil (3/6); surg res (3/6)	Trach-br rem (3/6)
Murphy et al (1995)[5]	3	Surg res (3/3)	Trach-br rem (1/3); fib-mus thick (2/3)
Newman and Bender (1996)[6]	18	Esoph dil (6/18)‡; surg res (2/18)§	Fib-mus thick (2/18)
Sarihan and Abes (1997)[7]	3	Esoph dil (2/3); surg res (1/3)	Mem diaph (3/3)
Diab et al (1999)[8]	6	Esoph dil (2/6); surg res (4/6)‖	Trach-br rem (1/6); fib-mus thick (1/6)¶

Abbreviations: esoph dil, esophageal dilatation; surg res, surgical resection; trach-or rem, tracheobronchial remnant; mem diaph, membranous diaphragm; fib-mus thick, fibromuscular thickening.

*This is a report of only pathology or surgically confirmed diagnoses.

†One of the 9 underwent surgical drainage caused by dilatation perforation.

‡Five of the 6 had an esophageal perforation secondary to dilatation; 3 were treated with surgical repair or drainage, and the remaining 2 were treated medically.

§One of these 2 patients underwent surgical resection due to dilatation perforation.

‖One of 4 had an esophageal perforation secondary to dilatation, which was treated conservatively, and the patient later underwent surgical resection.

¶The 2 other patients who had surgical resection had pathology reported as "normal."

STRICTURE in EA-TEF

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of Patients
Patient Characteristics</th><th>Symptoms of Congenital Esophageal Stenosis (CES)</th><th>Diagnosis of CES</th><th>Treatment of CES and Outcomes</th><th>Conclusion</th></tr>
<tr>
<td>Michaud et al (16)
2013</td>
<td>Retrospective Review
18 years review of 38 centers of the French Network on Esophageal malformations and congenital disease</td>
<td>61 patients
30M 31F
Mean age at diagnosis 2yrs (1day-14yrs)
7 (11%) were diagnosed >5yrs

29/61 (48%) CES were associated with Type C EA

Mean age at diagnosis of CES + EA was 7months vs 124months in isolated CES (p<.05)</td>
<td>21 (34%) were asymptomatic

40/61 (66%) presented with symptoms at mean age of 39mths (1-166)

Common symptoms were:
Dysphagia 50%
Food Impaction 50%
Repeated vomiting 40%

In 6 CES was diagnosed during endoscopy for retained foreign body

Respiratory Symptoms in 27%;
Respiratory failure
Dyspnea

At diagnosis 35% were malnourished (z score weight for height <2SD)

Vomiting/food impaction/impaired growth were more often seen in isolated CES vs EA + CES (p<.05)</td>
<td>18/29 with EA were diagnosed at time of repair of EA or at time of contrast study
In 3 with EA the diagnosis was incidental
In 1 at time of passage of NG tube
2 at endoscopy for follow up of EA

Barium study identified CES in 56/61 (91%)

Endoscopy done in 50/61 (82%) confirmed diagnosis

Endoscopic ultrasound done in 1

Location of CES
<table>
<tr><th></th><th>Upper Esophagus</th><th>Middle Esophagus</th><th>Lower Esophagus</th><th>Cardia</th></tr>
<tr><td>Isolated CES 32</td><td>6 (19%)</td><td>6 (19%)</td><td>18 (56%)</td><td>2 (6%)</td></tr>
<tr><td>CES+EA 29</td><td>0</td><td>6 (21%)</td><td>22 (76%)</td><td>1 (.04%)</td></tr>
<tr><td>All Patients 61</td><td>6 (10%)</td><td>12 (20%)</td><td>40 (65%)</td><td>3 (5%)</td></tr>
</table>

CT scan (CTS) done in 8 and confirmed diagnosis but did not show any TBr in esophageal wall

Pathology of stenotic segment done in 18 at time of surgery
TBR seen in 12
Fibromuscular thickening 6
In absence of histological evidence of TBR and endoscopic diagnosis of membranous stenosis (MS), FMS was presumed to be present in the rest:
TBR 16
FMS 40
MS 5

None had multiple CES

MS not seen in association with EA</td>
<td>Treatment and outcomes shown in Figure 3

Data missing for 3 lost to F/U after initial diagnosis

Endoscopic dilatation done using :
Savary bougienage (39 Sessions)
Balloon dilatation (103 sessions)

Median number of dilatations/patient was 2.5 (1-11)

16 had bougienage (3-5/patient)
35 had balloon dilatation (2-11/patient)
2 had both
Perforation in 2 (3.4%)
1 after bougienage and 1 after balloon dilatation
Both needed surgical resection of CES and 1 needed coloplasty

13/49 (27%) were asymptomatic after endoscopic dilatation
36/49 (73%) had persistent symptoms of moderate to severe dysphagia
15 (30%) had additional surgery

9 (16%) had first line surgery and 4 became asymptomatic
5 had dysphagia at 1-18yrs follow up

Surgery involved resection and end to end anastomosis

In patients with persistent dysphagia symptoms due to stricture could not be separated from those secondary to dysmotility</td>
<td>Largest reported study on diagnosis and treatment outcomes of CES

Food impaction was the classical symptom of CES but may be preceded by FTT, dysphagia and aspiration pneumonia

CES associated with EA was diagnosed at time of EA repair in only 62% and hence diagnosis can be delayed. CES should be considered when dysphagia and food impaction persist in EA patients. A barium study can be helpful in these circumstances

Conservative treatment with endoscopic dilatation is the first line treatment in most cases

Persistent dysphagia could be due to failure of dilatation of esophageal dysmotility

All TBR patients needed surgery (first or second line) in this series and both perforations occurred in TBR patients. Hence dilatation may be effective in patients with FMS or MS CES but surgical repair is often required for TBR CES.

Regardless of treatment option dysphagia can persist and CES patients need to be followed up long term

CTS is not a good method to differentiate between TBR-CES and FMS-CES</td>
</tr>
</table>

					Median follow up 33 months (1month-20years) dysphagia seen in 37/58 (64%) regardless of treatment The incidence of dysphagia did not differ between the group with CES+EA 10/29 vs isolated CES 7/32, p=.27 All 15 with TBR had surgery 10 had dilatation prior to surgery	

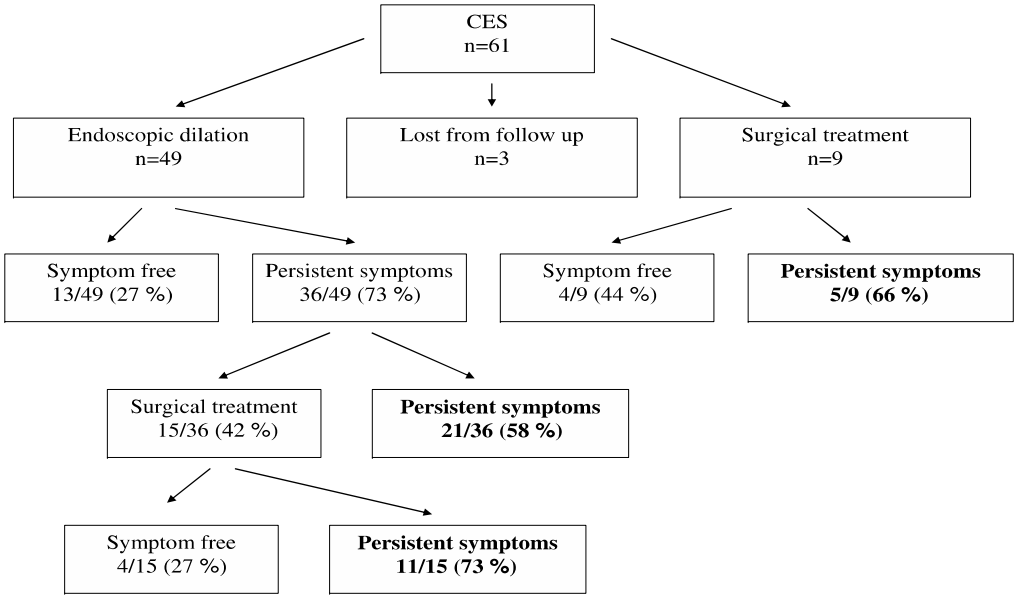

Figure 3 Treatment and outcomes.

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Results of Balloon Dilatation of strictures	Conclusion
Lisy et al (17) 1998	Prospective case cohort study	24 patients with esophageal stricture **10 with EA-TEF** 5 Achalasia 3 GER 3 Corrosive strictures 1 post radiation 2 CES **Method** Fluoroscopically guided angioplasty balloon dilatation of esophageal strictures. Catheters inserted trans nasally. Balloons inflated 3 times for 8minutes each. 8/2/15/18 or 22mm diameter balloons used. Dilatation repeated if dysphagia recurred. If no improved surgery was done. Success defined as resolution of dysphagia a year after dilatation	100 dilatation procedures Results of dilatations shown in Table 1	Long term success was seen in 63% of cases at 1 year post dilatation Balloon dilatation was a successful method for esophageal strictures associated with EA-TEF or GERD High initial success rate decreases with time Improvement in dysphagia was more striking and longer lasting if dilatation was combined with anti reflux medication in strictures in EA-TEF and GERD patients

STRICTURE in EA-TEF

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of Patients
Patient Characteristics
Methodology</th><th>Stricture grading
Stricture symptoms
Results of endoscopic dilatation of strictures</th><th>Risk factors for development of strictures</th><th>Conclusion</th></tr>
<tr>
<td>Parolini et al (18)
2013</td>
<td>Retrospective longitudinal study
2004-2012</td>
<td>35 consecutive EA patients
27 (77.1%) Type C EA
5 (14.3%) Type A EA
3 (8.6%) Type B EA

Mean follow up 101+/-71.1months (7.8-232.5) median 97.6
Num available for assessment:
1 yrs 34
2 yrs 28
3 yrs 21
5 yrs 13

Asymptomatic children followed up at 3, 6,12 months and 2, 3, 5 years

Endoscopy and pH Metry at 1 year

Mean gestational age 37.1 (34.2-40.3)
Mean BW 2.440 (1.580-3.510)
24M 11F
Associated anomalies 24 (68.6%)

Long Gap 8 (22.9%)
Long gap defined as >6 vertebral body gap

Anastomotic tension 10 (28.6%)

Anastomotic Leak 3 (8.6%)

Recurrent Fistula 1 (2.9%)

Tracheomalacia 2 (5.7%)

PPI therapy was routine and ceased in absence of symptoms or normalization of pH Metry and endoscopy</td>
<td>Routine esophagography in second post op week (12.7days, range 6-25
Stenosis detected in 12 (34.3%)

Endoscopy at 1 month
Degree of stricture assessed endoscopically according to Stricture Index (SI)
SI=(D-d)/D
D=Largest diameter of esophageal pouch
D= Stricture diameter

Group 1 SI<0.1
(no evidence of stricture)
Group 2 0.3>SI>0.1
(Mild stricture, endoscope passed with difficulty)
Group 3 SI >0.3
(Tight stricture not crossable by endoscope)

Symptoms
Dysphagia
Vomiting
Cough
Foreign body obstruction
Recurrent chest infections
Poor weight gain
If symptoms present contrast done to confirm then endoscoped to assess severity

No routine prophylactic pneumatic dilatations done

Stricture Incidence post EA Repair

<table>
<tr><th></th><th>Patients n</th><th>Strictures N (%)</th><th>Dilatations n</th></tr>
<tr><td>1 month</td><td>35</td><td>20 (57.1)
Gp 1:7 (35)
Gp2:10 (50)
Gp3: 3 (15)</td><td>4
0

1

3</td></tr>
<tr><td>3 months</td><td>35</td><td>18 (51.4)</td><td>1</td></tr>
<tr><td>6 months</td><td>35</td><td>18 (51.4)</td><td>7</td></tr>
<tr><td>1 year</td><td>34</td><td>16 (47.1)</td><td>1</td></tr>
<tr><td>2 years</td><td>28</td><td>12 (42.9)</td><td>4</td></tr>
<tr><td>3 years</td><td>21</td><td>8 (38.1)</td><td>5</td></tr>
<tr><td>5 years</td><td>13</td><td>5 (38.5)</td><td>8</td></tr>
</table>

20 children had a cycle of 30 dilatations
Mean 1.5 (0-8)</td>
<td>Table shows risk factors associated with development of strictures
GERD
Anastomotic tension
Long gap (LG)

<table>
<tr><th></th><th>Stricture N (%)</th><th>No stricture N (%)</th><th>P Pearson</th></tr>
<tr><td>LG 8</td><td>7 (87.5)</td><td>1 (13.5)</td><td>0.008</td></tr>
<tr><td>Tension 10</td><td>8 (80)</td><td>2 (20)</td><td>0.02</td></tr>
<tr><td>GERD 16</td><td>12 (75)</td><td>4 (0.25)</td><td>0.004</td></tr>
</table>

Compared to EA Type C, Type A and B had an increased risk for stricture formation and dilatation
Type A HR 3.791
Type B HR 2.301</td>
<td>Anastomotic stricture is common post EA repair. 57.1% had endoscopic evidence of stenosis at 1 month

Endoscopy has a higher sensitivity for diagnosing stricture compared to radiography

GERD, anastomotic tension and long gap EA have increased risk for developing anastomotic stricture

Stricture Index at 1 month can predict severity of stricture and need for and number of subsequent dilatations in future. Patients with tight stricture (Group 3) had a higher hazards ratio for needing dilatations compared to those with mild or no stricture

EA Type A and B which have a higher gap length had an increased stricture risk and need for dilatations

Majority of patients needed no more than 3 dilatations, apart from those with severe GERD

No perforation was seen during endoscopic dilatation

Limitations of study include lack of uniformity in follow up due to retrospective nature and low number of samples in some groups</td>
</tr>
</table>

			Compared to group 1 remaining groups had increased risk for dilatations,p=.001 Hazard Ration (HR) for group 2 2.291 and HR for group 3, was 12.765 Majority 16/20 (80%) presenting with mild stenosis needed only 1 dilatation The remaining children had severe GERD **Table 3 shows number of dilatations according to stricture index groups**		

Table 3 Number of dilatations according to stricture index groups

Groups	*N*	Dilatations, mean	Min	Max	SD	Hazard ratio	SE	95 CI %
1	7	0.5	0	5	1.446	1.000	1.030	0.03–3.25
2	10	1.1	0	7	2.392	2.291	1.409	0.685–7.653
3	3	3.67	2	8	2.251	12.765	9.231	3.093–52.671

SD standard deviation, *SE* standard error, *CI* confidence interval

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients with distal esophageal stenosis (DES) with esophageal atresia	Results	Conclusion
Thomason et al (19) 1987	Case Series	3 had distal esophageal stenosis with EA All had Type C EA	In all 3 cases DES was diagnosed by post operative routine contrast study DES was subsequently confirmed at endoscopy In all 3 patients the DES was treated with dilatations and surgical resection was not needed	Congenital esophageal stenosis (CES) is usually not seen during repair of EA At time of this study 24 EA patients with CES had been reported. Histology was known in only 5 (3 had TBR, 1 was normal and 1 showed fibrous tissue). Symptoms of CES include recurrent chest infections in 9, anastomotic leaks in 3, foreign body impaction in 5. 21/24 patients had associated EA and in 17 where the Type of EA was mentioned had Type C EA., Type was seen in 2 and Type E in 2. CES is usually diagnosed at fluoroscopy CES often results in symptoms when patient is started on solids There are 2 types of CES, membranous and segmental. The segmental can be due to tracheobronchial remnants (TBR) or fibromuscular (FMS). The FMS ones are usually 104cms long, have hourglass configuration and located at junction of middle and lower thirds of esophagus. They can often be dilated without difficulty. The TBR ones are more distal have more severe obstructive symptoms and often need surgery Early diagnosis during fluoroscopy and treatment with initial dilatations where indicated may prevent complications

STRICTURE in EA-TEF

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of Patients
Patient Characteristics</th><th>Results of endoscopy guided balloon dilatation strictures (EGBD)</th><th>Conclusion</th></tr>
<tr>
<td>Tam et al (20)
1991</td>
<td>Prospective case cohort study
1986-1990</td>
<td>33 patients with strictures
Mean age 3.7years (3weeks-20 years)
18 had esophageal strictures:
13 EA patients
5 GERD patients

13 had anastomotic strictures following esophageal replacement
12 Colon
1 Stomach

2 had caustic strictures

23/33 had failed to respond to bouginage (mean 11.2 sessions, range 1-32

All had contrast studies prior to EGBD</td>
<td>
<table>
<tr><th>Stricture</th><th>No of patients</th><th>Mean EGBD Per patient (range)</th><th colspan="3">Response
Excellent Moderate Failed</th></tr>
<tr><td>Esophageal</td><td>18</td><td>2.2 (1-7)</td><td>14</td><td>4</td><td>0</td></tr>
<tr><td>Replacement</td><td>13</td><td>2.1 (1-6)</td><td>10</td><td>3</td><td>0</td></tr>
<tr><td>Caustic</td><td>2</td><td>1.5 (1-2)</td><td>0</td><td>0</td><td>2</td></tr>
</table>
4 did not respond to EGBD before GERD was treated but responded to EGBD after fundoplication

Both patients with caustic strictures had perforation complicating EGBD

Patients experienced less pain with EGBD and resumed solid feeding earlier compared to bouginage
</td>
<td>Advantages of EGBD:
Uniform radial force rather than axial shearing force of bouginage

Efficacy of dilatation is monitored fluoroscopically and end point need not be assumed

As balloon catheter is introduced in deflated state size of oro-pharynx is not a limiting factor

Placement of catheter under direct vision reduces risk of false passage of dilator

Tortuosity, angulation and redundancy of conduit in colon replacement is not a limiting factor

No need for gastrostomy and string placement for Tucker's dilatation

Placement of guide wire under direct vision reduces risk of perforation

EGBD is safe for esophageal and replacement strictures. It is not indicated for caustic strictures

Young age is not a contraindication for EGBD</td>
</tr>
</table>

				After EGBD patients were in less pain and eating sooner compared to bouginage As during dilatation may trachea may be compressed GA and endotracheal intubation is recommended In presence of stricture GERD may not be evident until after dilatation. Effective treatment of GERD is essential as an adjunct to EGBD in patients with GERD

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Stricture	GERD	Respiratory complications Tracheomalacia	Nutrition	Conclusion
Sri Paran et al (21) 2007	Retrospective Review 1977-2004	26 Type A pure EA patients 3 died prior to surgery 2 had esophageal replacement These 5 were excluded 11M 10F Maternal history of hydramnios 10)48%) Mean Apgar score at 1min 6 Mean Apgar score at 5min 9 Associated anomalies 62% Median gestational age 35.5wk (28-42) Median BW 2.6kg (1.2-3) Median initial gap 3.7cm (2.5-5.5) Median preoperative gap 1.5cm (0.5-2.5) Circular myotomy done in first 7 Median age at delayed primary anastomosis 80days (35-270) Gastrostomy done day 1-3 Median hospital stay 5.5mths (2-14) Median Follow up 13.5yrs (28mths-27yrs) Questionnaire and personal or telephone interview in all survivors 4 deaths (19%) prior to 1980	16/21 (76%) developed stricture Between 2-17 dilatations over 2 years If symptoms persist post dilatation or diameter is decreasing resection anastomosis done 6 (28.5%) had resection anastomosis between 8 months-3.5 years 2 of these patients had fundoplication 9 strictures associated with GER, all had fundoplication	14 (66%) had symptomatic GERD 9 (43%) needed fundoplication 5/9 who needed fundoplication had hiatal hernia GOR persisted after Thal fundoplication and needed Nissen 1 Nissen needed redo 2 (9.5%) had Barrett's. Both had fundoplication are followed up with endoscopy Severe esophageal dysmotility seen in contrast study in 7 patients (33%) who had myotomy	2 (9.5%) had undiagnosed fistula which was ligated Aortopexy done in 2 (9.5%) for tracheomalacia	Gastrostomy feeds stopped after median period of 50 days (14-255) 15/17 (88%) surviving children were on normal diet 1 with Downs and 1 with oral aversion were on gastrostomy feeds Median weight was on 20th percentile (<P3-P50) Median height was on 50th percentile (<P3-P90)	GERD was diagnosed in majority (66%) of Type A EA patients who had a delayed anastomosis, and of these majority (64%) required fundoplication Barrett's patients need regular surveillance endoscopy even after fundoplication High incidence of strictures (76%) in pure EA patients and 28% needed resection. Early fundoplication was recommended for GER symptoms when anastomotic stricture was noted Only 1 patient with pure EA with initial gap length of 2.5cms had no subsequent problems in this series Long term outcome of pure EA patients managed by delayed primary anastomosis is satisfactory. 90% were eating normally and had acceptable growth

STRICTURE in EA-TEF

Author/Year	Study Type	Number of patients Patient Characteristics	GER	Stricture	Outcome using Prognostic Classifications Systems	Conclusion
Zhang et al (22) 2010	Retrospective Review 2006-2009	48 EA patients 33M 15F Mean gestational age 36 weeks (28-38) Average BW 2668g (1700-3800) 2 premature Associated anomalies 17 (35%) **EA Types** Type C EA 47 Type A EA 1 Type A EA needed colonic interposition **Preoperative evaluation:** Esophagography CT imaging 3D Graphic reconstruction of the esophagus Median follow up 18 months (4-28) **Post operative complications:** Pneumonia 6 (13%) Anastomotic leakage 7 (16%) Wound sepsis 5 (11%) 3 deaths Recurrent TEF 1 Delayed TEF 3 (7%)	GER 31 (67%)	Anastomotic stricture 4 (10%) Main symptoms: Dysphagia Sialorrhea Recurrent chest infections Treated with balloon dilatations under yray guidance 3-4 dilatations/stricture Oral feeding introduced 4-6 hours after dilatation No perforations	6 deaths overall Total mortality 12.5% **Comparison of survival in study with other major prognostic classification systems shown in Table 4** Minimum BW was 1700 so relationship between BW and mortality could not be explored using traditional classification system, and Montreal classification was used	Esophagography combined with CT imaging and 3D graphic reconstruction helped evaluate defect in esophagus accurately and plan appropriate surgery. Helped evaluate distance between esophageal end, development of distal pouch and location and diameter of TEF accurately.. However the limitations of this method are that it can be used only for Type C EA when stomach, distal pouch and TEF are filled with air. There is also radiation exposure to infant. High GER rate could be due to short follow up Stricture rate was low at 10% and authors thought this was due to meticulous handling of esophageal ends, preservation of blood supply, use of 6 o Monocryl suture material, inclusion of mucosa in every suture at anastomosis. Most patients had excellent short to mid term outcomes

Table 4 Comparison of our survival with the major prognostic classification systems

Classification	Published survival	Our data		
		n	Death	Survival rate
Waterston et al				
A	95%	29	0	100%
B	68%	13	4	69%
C	6%	6	2	67%
Montreal				
I	93%	37	2	95%
II	31%	11	4	64%
Spitz et al				
I	97%	33	2	94%
II	59%	15	4	73%
III	22%	0	–	–
Bremen				
Without complications				
I	100%	21	2	90%
II	50%	7	1	86%
III	0%	0	–	–
With complications				
I	33%	12	1	92%
II	40%	8	2	75%
III	0%	0	–	–

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Results of Balloon Dilatation of Esophageal Strictures	Conclusion
Yeming et al (23) 2002	Prospective case cohort study 1994-1998	20 patients age 17days-12years **2 Groups** **Group A 10** **EA 10** **Group B 10** Caustic ingestion 7 Tight fundoplication 2 Peptic stricture 1 No prior bouginage was done before Balloon Catheter Dilatation (BCD) Indication for BCD: Dysphagia Excessive drooling unrelated to eating Regurgitation of food Regression in tolerance of food caliber Discomfort with oral intake (chest pain) Symptomatic children had barium study and endoscopy prior to BCD General anesthesia not used for BCD Fluoroscopy and angiographic wire guidance was used BCD done once a week for severe strictures and then ½-3 weeks over time depending on recurrence of symptoms Balloon sizes gradually increased Post BCD contrast study was done Follow up 6-42 months All patients had barium or endoscopy to confirm clinical resolution **Outcome measures:** Number of dilatations Perforations Success or failure of BCD Success defined as increasing intervals of age appropriate food tolerance between dilatations Failure defined as abandonment of BCD for surgery	20 children had 126 BCD 17/20 (85%) had successful BCD In Group A 100% had complete resolution of symptoms. Number of dilatations median 2 (1-4) over average time of 2 months Follow up 6-42 months In Group B 7/10 (70%) had success with follow up 6.5-36 months Number of dilatations 3-40 with periods ranging from 2-30 months 4/7 (57.1%) with caustic ingestion were dilated successfully All 3 failures eventually needed esophageal replacement There was 1 perforation in this group Both children with tight fundoplication and 1 with peptic stricture were dilated successfully **Data shown in Table 1**	All strictures in EA patients were treated successfully with BCD Highest failure rate with caustic ingestions 14.3% perforation in caustics in this study BCD is an effective treatment for esophageal strictures in children, but has a higher complication and failure rate in caustic ingestion

Table 1. Balloon Catheter Dilatation in Children With Esophageal Strictures

	No. of Patients	No. of Dilatations	Treatment Period (mo)	Treatment Results		
				Success	Failure	Perforation
Group A						
Esophageal atresia	10	(1-4)*	(1-2)	10		
Group B						
Caustic ingestion	7	(3-40)	(2-30)	4	2	1
Tight fundoplication	2	(3-4)	(1-2)	2		
Peptic stricture	1	4	2	1		
Totals	20	126†		17 (85%)		1 (5%)

*Range of number of dilatations and treatment period.

†Total number of dilatations in 20 children.

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	GER	Stricture Results of Dilatation	Risk factors	Conclusion
Serhal et al (24) 2010	Retrospective longitudinal study 2000-2005	73 EA patients 11 excluded 9 Ladd Gross EA Type 1 2 early mortality 62 patients included 61 were EA Type III 1 was EA Type V Repair 1st day 22 2nd day 37 3rd day 3 Data collected on sex, BW, gestational age, anastomotic tension, duration of trans anastomotic/thoracic tubes, anastomotic leakage, recurrent TEF GER (symptoms, pH metry, endoscopy) In presence of esophagitis anti reflux treatment was optimised stricture symptoms (dysphagia, vomiting, cough, slow feeding, foreign body/food bolus obstruction, chest infections, poor weight gain) Those with stricture symptoms had contrast study and if stenosis was diagnosed an endoscopy No prophylactic dilatation was done Dilatations done with Savary Gilliard bougies (5,7,9,11,12.8,15mm) Dilatations considered successful when adequate lumen was achieved with relief of dysphagia and weight gain/growth Characteristics of patients with anastomotic stricture was compared to those without stricture	48/62 (77%) had symptoms of GER This was confirmed by pH Metry/endoscopy 26 (42%) had esophagitis Esophagitis seen in 61% with stricture vs 31% without stricture, p<.05 Patients with confirmed patients were given Prokinetic/PPI 13 patients medications failed 11 had Nissen fundoplication 3 had esophagogastric disassociation (Bianchi) Surgery for GER done in 34% with stricture vs 13% without stricture, p<.05	23/62 (37%) had anastomotic stricture Time for first dilatation mean 149 days (30-600) Stricture resolution after mean 3.2 dilatations (1-7) Over mean 7 months (0-55) 4 (17%) had 1 dilatation 5 (21%) needed 4 or more Mitomycin applied in 1 after 7 dilatations Mean follow up after last dilatation was 47 months (8-86) Dilatation successful 20/23 (87%) 3 unsuccessful 1 mild dysphagia 2 severe dysphagia Both due to dysmotility These patients had Bianchi procedure due gastric pull up in 2 and small stomach in 1 1 had nutrition via PEG 1 ate orally No complications with dilatations 2 had CES, 1 had surgery, other had 3 dilatations	Significant relationship between stricture formation and: Prematurity p=.035 VACTERL p=.013 GER p=.029 Anastomotic tension p=.024 Anastomotic leakage p=.043 Stricture was unaffected by: Sex IUGR Tracheomalacia Duration of intubation Use of Curare per operation Duration of trans anastomotic tube and transthoracic drains Multivariate analysis: Only anastomotic tension was significant OR 9.23, p<.0024	Anastomotic stricture is frequent after EA repair with a rate of 37% in this study Anastomotic tension was the only factor which increased risk for stricture by 9. It was better predictor for stricture formation than gap length in EA types III and V GER was not a significant predictor on multivariate analysis for stricture formation probably because of increased use on PPI Dilatation only done in symptomatic patients and was successful in 87%. There was no complication after bougie dilatation in this study Data suggest esophageal dilatation with Savary Gilliard bougie is an safe and effective procedure to treat EA anastomotic strictures

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Results of endoscopic treatment of congenital esophageal stenosis (CES)	Conclusion
Romeo et al (25) 2011	Retrospective Review 1980-2010	47 consecutive patients had CES 27F 20M Mean age 28.3 months (1day-146months) 8 (17%) had Downs 15 (32%) had Type C EA Symptoms: 32 (68%) had dysphagia with regurgitation 5 (10.6%) had solid food refusal 10 Asymptomatic Diagnosis Barium Study in 34 (72.3%) Confirmed by endoscopy 13 (27.7%) Location All had CES in distal esophagus 1 in mid esophagus EUS mini probe used to differentiate between TBR CES and FMH CES EUS done in 12 TBR 6 FMH 6 Dilatations done with Rigiflex balloon under fluoroscopy and GA (8,10,12mm) Savary Gillard dilators (7,9,11,12.8mm) were used from 1990 Between 1990-1997 bot dilators were used After 1997 only Savary Gillard dilators were used Patients had dilatations every 15 days till stable diameter of 9-12.8mm Frequency depended on age, swallowing difficulty and stability of lumen size achieved All got ranitidine and from 1990 omeprazole 1mg/kg for 1 month Follow up Clinical review Contrast study Endoscopy + biopsy pH Metry to detect stricture and GER Perforation rate evaluated	148 dilatations in 47 patients 32 hydrostatic dilators 116 Savary dilators Mean number of dilatations 3/patient (1-9) 1 had membranous web which was resected endoscopically Complications: 5 had perforation during first dilatation 3 (9.37%) after hydrostatic dilatation 2 (1.7%) after Savary dilatation Difference in complication rate was significant RR 6.3, OR 5.9, p=.03 Complete resolution of stenosis and symptoms in 45 (95.7%) after mean follow up of 9.6yrs (1.3-29) 1 Downs patients with FMH CES required laparoscopic myotomy 1 with TBR CES required resection of stenosis and Nissen fundoplication 1 had anastomotic leak In follow up 6 (3/6 had EA and peptic strictures) had fundoplication	CES is rarely diagnosed in neonates. Symptom onset is often with solid foods. EUS helps to distinguish between TBR and FMH CES Surgical treatment of CES includes segmental resection with end to end anastomosis or longitudinal myotomy for FMH type Anastomotic cicatricial strictures, anastomotic leaks and GERD are common complications due to esophageal tension Endoscopic treatment can be done with Savary or hydrostatic dilators. Although hydrostatic dilators provide a radial rather than an axial shearing force they can result in perforation due to sudden “crack” of stenosis. It is prudent to dilate to only 2-3mm larger than size of first dilator that meets resistance An endoscopic visualization after dilatation is important as is contrast study to exclude perforation Conservative treatment with dilatations was effective in 95.7% irrespective of subtype of CES 5/6 patients with TBR CES by EUS are asymptomatic at follow up Initial management of all CES should be by dilatations with surgery reserved for those who fail conservative management GERD can add morbidity after surgery leading to stricture. This was seen in 6 of the dilated patients in this study. Fundoplication may be needed to treat GERD

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Results of Balloon Dilatation of strictures	Conclusion
Sandgren et al (26) 1998	Retrospective Review 1983-1994	36 patients EA 28 TEF 3 CES 1 Peptic stricture (GERD) 1 Caustic ingestion 3 15F 21M Stricture suspected because of symptoms and confirmed by contrast study Balloon dilatation was initially done at a few weeks interval and subsequent timing was determined by symptoms, size of lumen and success achieved with each dilatation Age at treatment 2weeks-15years	Number of strictures 39 Number of dilatations 171 Balloon catheterization revealed stricture in all but 1 case Findings on contrast study correlated well to those on balloon catheterization although the latter did not confirm the need for dilatation in all cases of moderate narrowing seen in contrast study Average number of dilatations 5 Average period of treatment mean 3 months (1day-6years) Balloon dilatation was successful 31 (79%) 2 cases changed to bouginage 6 strictures were resected No obvious difference in underlying diagnosis Complications: Rupture with leakage 6 Catheter perforation 2	Balloon dilatation is effective, safe and successful for esophageal strictures and should be tried first for esophageal strictures and bouginage or surgical resection undertaken only if it fails. It involves radial forces and gives better control as fluoroscopy is used No obvious difference in duration of treatment according to underlying diagnosis was seen

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Strictures	Fluoroscopic Balloon Dilatation (FBD)	Stent Placement Surgery	Conclusion
Thyoka et al (27) 2014	Retrospective Review 1999-2011	103 EA patients with strictures 61 (59%) Male FBD done under GA by interventional radiology service Post dilatation contrast study was done if there was difficulty crossing the stricture with guide wire, excessive bleeding on withdrawal of the balloon, severe tachycardia or abrupt complete inflation of the balloon. Perforation was defined as a major complication **Technical Success** was defined as a >50% increase in the diameter of the stricture **Clinical Success** was defined as achievement of a lumen adequate for relief of obstructive symptoms, weight gain and absence of procedural complications **Outcomes** were number and frequency of dilatations, clinical response to dilatations, perforation, requirement for surgery and mortality Median follow up 1.9 years (0.5-11)	103 strictures in patients 95/103 (92%) had single stricture 8/103 (8%) had>1 stricture (2 strictures 7, 3 stricture 1) Median stricture diameter 5.5mm (0-14) Median stricture length 4mm (1-65) Commonest vertebral level of stricture T4 (n=53, 52%)	103 patients required 378 FBD 1 or more FBD procedures produced clinical success in 93 (90%) In 44 (43%) complete resolution of symptoms after the first dilatation 59 (57%) had need for further dilatations 15 (14%) needed >5 dilatations There was no difference in the proportion of patients who needed just 1 dilatation and were younger than 1 year vs those who were >1 year of age, p>.99, OR1.07 Symptoms recurred at median time of 24 months 2 patients had 4 perforations Perforation rate 4/378 (1%) No mortality 18 (17%) required Nissen fundoplication for GERD	10 (10%) had failure of FBD Stent was placed in 3 2 required reconstructive surgery for stent complications Reconstructive surgery also done in another 4 3 has resection of stricture All 10 who had surgery did so after ten or more FBD Indications for surgery: Stent complications Uncontrolled GERD Recurrent stricture affecting QOL Complications of FBD (perforation and sepsis) Failure to thrive	Largest series of FBD in EA patients with symptomatic anastomotic strictures In EA patients with strictures fluoroscopic balloon dilatation (FBD) is successful in 90% Half of the patients undergoing FBD will require 2 or more dilatations to achieve complete relief There is no difference in the proportion of patients who require 1 dilatation for complete relief between the groups under and over the age of 1 The need for >10 FBD sessions is a predictor of the need for surgery Perforation rate after FBD is minimal (1%) and most of the perforations can be treated conservatively 17% of EA patients with strictures had symptomatic GER and required fundoplication

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Results of balloon dilatation of anastomotic strictures in EA patients	Conclusion
Said et al (28) 2003	Prospective case cohort descriptive study 1998-2001	25 EA patients 15M 10F Median age 4 months (1-36) All were Type II EA In early contrast swallow done between 7-10 post operative day no stricture was seen Stricture subsequently suspected if: Swallowing difficulties Vomiting All had Barium swallow to confirm stricture/location/severity If GER seen in swallow medical treatment started prior to balloon dilatation **GER seen in 15 (60%)** Initially treated with medication 11 cases of treatment failure had Nissen Fundoplication during or after balloon dilatation sessions Selected strictures: >50% of esophageal lumen **Stricture Index** SI = A-a/A A: diameter of esophageal lower pouch A: stricture diameter Balloon dilatation done under sedation and fluoroscopic guidance Diameter of initial balloon was 203mm larger than stricture First dilatation done with 4-6mm balloon If dilatation was easy size of balloon increased by 2mm in same session Subsequent weekly sessions until final diameter SI <10% was achieved Post dilatation contrast injected to look for perforation Patients were allowed feeds/soft diet 2 hours later	Stricture rate 25/98 (25.5%) Stricture >50% of esophageal lumen in all cases Dilatation successful in all after total of 115 dilatations Median 4 (1-14)/patient **Prognostic Factors for success of dilatation:** A requirement of 2 or fewer dilatations was significantly associated with an age <6months (RR 0.52) Likelihood of requiring 2 or less dilatations was 12 times higher for patients without GER than those presenting with GER, p<.001 **Complications:** Perforations 2/115 (1.7%) No significant predictive factors were found for complication Both treated conservatively Follow up 4-33months All patients were symptom free	Fluoroscopically guided balloon dilatation is a safe and effective treatment for anastomotic strictures especially in EA patients under 6 months of age and without GER Balloon dilatations performed in EA patients under the age of 6 months required less dilatations as there was less scar tissue and fibrosis However there is risk in doing first dilatation less than 3 weeks post EA repair due to perforation risk Children without GER were 12 times more likely to require less than 2 dilatations/stricture GER is also associated with higher risk for perforation post dilatation. Both patients who had perforation had GER Early treatment of GER is important Suggestions to reduce risk of perforation: Use of balloon longer than stricture Balloon diameter adjusted to stricture size Gradual increase in balloon size and avoiding dilating esophageal lumen to maximal diameter in 1 session Choose weekly interval between sessions Pressure must not go beyond 3ATM Avoid manipulation of inflated balloon in esophageal lumen Early detection of perforation using water soluble contrast post dilatation Early treatment of anastomotic strictures and detection of GER suggests routine Barium Swallow performed 4 weeks post EA repair is helpful in planning appropriate management

		Success: if SI decreased on oesophagogram to at least 10% No swallowing difficulties for upto 3 months after dilatation Good weight gain and growth Successful end point was relief of stricture in 2 or fewer dilatations		

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Balloon Dilatation Results	Bouginage Results	Results in patients who had both bouginage and balloon dilatation	Conclusion
Lang et al (29) 2001	Retrospective Review 1984-2000	34 EA patients with symptomatic anastomotic strictures Group A 16 patients who only had balloon dilatation Group B 6 patients who had initial unsuccessful bouginage followed by balloon dilatation subsequently Group C 12 patients who only had bouginage All patients received antibiotic prophylaxis Median time between EA repair and first dilatation or bouginage was 14 days	Group A 16 patients had52 dilatations Median age at first dilatation 0.27 years (0.09—9.9) Median weight 3.3kg (2.1-22) Done under sedation with endoscopic and fluoroscopic control Balloons inserted beside endoscopes or over guide wire Balloons used: Rigiflex 12/15/18/20/25mm Maxforce 6/8/18mm Mansfield 6mm VACS 7/10mm For newborn 6-8mm used Maximal pressure maintained from 30/60 seconds to 3-5min No further effect if prolonged beyond 5 min 22 patients (Group A+B) had 52 dilatations In all patients the dilatation was effective and endoscope was able to enter stomach easily. Patients became asymptomatic and were able to eat orally No effect on weight gain/growth as patients were dilated before stricture affected weight gain 10 needed only 1 dilatation Median 2 (1-7)/patient Conducted over a median period of 3 months (1-18) 17/22 (77%) had no more dilatations for a year and none are currently symptomatic Median follow up after birth 2.5years (0.4-13.1) Median follow up after last dilatation 2.5 years (0.2-6.5) Complication: 2 perforation 2/52 (3.8%) 2 compressions of trachea with desaturation	Group C Done in a retrograde manner with a Rehbein bougie over a gastrostomy under sedation 178 bouginages in 12 patients over 9 years Median 8.5 procedures (3-60) Median age at first bouginage0.21 years ((0.1-3) Median weight 3.5kg (2.6-13.3) The difference between the number of dilatations required and the number of bouginages required to achieve success was significant, p=.002 Data on complications not available Median follow up after birth 7 years (0.5-17) Median follow up after last bouginage 6.7years (0.2-16.5) Most patients are currently without symptoms	Group B 6 patients over 6 years who had 202 previous bouginages before undergoing dilatation Median 42 procedures (3-60) Median age at first bouginage 0.18 years (0.1-0.5) Median weight 3.7kg (2.4-5.1) Median follow up after birth 9.8years (4.2-21.3) Median follow up after last dilatation 3.4 years (1.7-4.9)	Compared with bouginage balloon dilatation of anastomotic strictures in EA patients is more effective and less traumatic Placement of balloon under direct vision avoids false passage of catheter. Efficacy of procedure can be visualized under fluoroscopy as can occurrence of complications like perforations Significantly less balloon dilatation procedures (median of 2) required compared to bouginage (median 8.5) for effective treatment of strictures Complications are rare and can be managed conservatively Balloon dilatations can be done even in small infants

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Results of treatment of Congenital Esophageal Stenosis (CES)	Conclusion
McCann et al (30) 2014	Retrospective Review 1990-2012	17 EA patients with CES Overall incidence of CES in EA is 3.6% 13M 4F 15 (88%) had Type C EA 1 (6%) had Type A EA 1 (6%) had Type E EA 7 had associated malformation Mean age at diagnosis 11.6months (1day-60months) Diagnosis: During EA surgery (1) Esophagogram (12) 71% 7 (41%) in first post operative contrast 5 (30%) on 2nd or 3rd esophagogram Endoscopically 4 (23%) CES distal to anastomosis in all Symptoms: Regurgitation Dysphagia Respiratory problems Growth retardation Food impaction 3 had TBR on histology	10 (59%) treated by dilatation only 1-3/patient 6/10 had hydrostatic balloon dilatation 4/10 had dilatation by bouginage 2/4 who had bouginage had perforation 1/6 who had balloon dilatation had perforation 6 (35%) had surgery because of failure of dilatations (4 each for balloon and buiginage dilatation) Failure of disappearance of waist under fluoroscopy was predictive of dilatation failure in ¾ who had balloon dilatation All 3 with TBR needed surgery 1 with membranous stenosis had perforation during bouginage and needed surgery	CES is frequently associated with EA A high suspicion for CES must remain in presence of EA As reflected by mean age at diagnosis (11.6 months) diagnosis of CES can be difficult Symptoms can be non specific. Slight preponderance of males (75%) and 2 with Downs in this series Al esophagograms in EA patients should be carefully evaluated for CES as CES can be misinterpreted as esophageal spasm, dysmotility or narrowing due to GER. In 30% CES was not diagnosed in first contrast study. Even with normal contrast study CES was diagnosed in endoscopy in 23% Dilatation was successful in majority (10/17) Failures commoner if TBR CES (6/7) Patients with known TBR or after failure despite 2-3 dilatations without disappearance of waist should be considered for surgery Perforation was frequent 18% (3/17)irrespective of technique of dilatation

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Stricture	Anastomotic Leaks	GER	Tracheomalacia Recurrent/Missed TEF	Deaths	Conclusion
Tsai et al (31) 1997	Retrospective Review 1975-1995	81 EA patients 46M (57%) 35F (43%) Mean gestational age 37 weeks (28-42) Mean BW 2443g (915-4035) Mean APGAR score at 1min 7, 5 min 8 **EA Types** Type A 7 (9%) Type B 1 (1%) Type C 67 (83%) Type D 1 (15) Type E 5 (6%) **Waterston Groups** Group A 24 (30%) Group B 31 (38%) Group C 40 (49%) **Associated anomalies** 24 (30%) **Associated GI anomalies** 14 (17%) Imperforate anus Duodenal Atresia Pyloric Stenosis Biliary Atresia Annular Pancreas **Surgery** 44 had primary anastomosis (within 48 hours) 7 had delayed primary anastomosis (median 9 days) 5 had repair of H type fistulas **Long Gap** 12 had staged repair of long gap Type A or C EA Esophageal anastomosis after bouginage 2 Colonic interposition 8 Staged esophageal lengthening 2 Long gap defined as gap length >2 vertebral bodies or >3cms Mean gap length in this group 4 vertebral bodies	Anastomotic stricture 25/62 (40%) Stricture defined as anastomotic narrowing in contrast study which required 1 or more dilatations Median number of dilatations 2 (1-9) 9/25 (15%) required >2 dilatations 9/25 with strictures had anastomotic leaks 9/12 (75%) patients with leaks developed strictures 5/25 with strictures (20%) also had GER Stricture rate in the staged repair group 5/11 (45) vs 20/51 (39%) for the primary and delayed primary repair groups These differences when looking at the leaks/GER and timing of repair were not statistically significant Stricture rate in esophagocolic (EC) anastomosis was 4/8 (50%) vs 21/54 (39%) in the esophagoesophageal (EE) anastomosis This difference was also not statistically significant All EE strictures were managed with dilatation,3/4 EC strictures needed anastomosis revision **Amongst 8 EC patients** Strictures 4/8 (50%) Leaks 6/8 (75%) Reoperation 5/8 (62%) Reoperation 3/8 (37%) for strictures 2/8 (25%) for graft	Anastomotic leaks in 12/62 (19%) Identified by presence of saliva in chest drain and confirmed by contrast study Leak rate in staged repair (long gap) was 6/11 (54%) vs 6/51 (11%) in primary and delayed primary repair groups, p=.004 The leakage rate for EC anastomosis 6/8 (75%) vs 6/54 (11%) for EE anastomosis was significant, p=.0003 3/6 (50%) EE leaks developed strictures which were managed by dilatation 5/6 (83%) EC leaks needed surgical revision for strictures or graft necrosis Leak rate between 1960-1974 10% Leak rate 1975-1995 19% Not significantly different	Documented by contrast study or pH Metry In 9 Diagnosed between 1month-6 years 6/9 treated medically 3/9 needed fundoplication	2 missed TEF (2.5%) Tracheomalacia 9 (11%) Diagnosed by bronchoscopy between 1month-3 years Dying spells 2 Treated by aortopexy 1 Tracheal stent 1	18/81 (22%) died 7 died before surgical intervention 4 died after preliminary staging 7 died after surgical repair Operative mortality 9/74 (12%) Late Mortality 2/74 (3%) Looking at those who had definitive correction of their associated anomalies Overall mortality 7/67 (10%) Operative mortality 5/67 (7%) **Comparing with historical group (1960-1974)** Overall mortality 22% Operative mortality 13% Late Mortality 2% After definitive repair 7% There was no significant difference between groups **Survival based on Waterston's criteria** Group A 100% Group B 89% Group C 11%	Incidence of anastomotic complications remains high Significant difference in leak rates in infants with long gap and staged repairs (54%) vs those with non long gap and primary repairs (11%). Although this could be due to anastomotic tension and gap length, the other explanation is 8/11 (72%) of patients with long gap and staged repair had colonic interposition and there was a higher leak rate in those with EC anastomosis (75%) vs those with EE anastomosis (11%). This high incidence of leak could be due to impaired blood supply in the cephalad end of the interposition graft. Leaks in EC patients also had a high (83%) reoperation rate High stricture rate of 40% could be due to the was strictures were defined, as only 15% required >2 dilatations Although difference in stricture rate between EC (50%) vs EE (39%) was not significantly different strictures in all EE patients were managed with dilatation where as 75% of EC strictures required anastomotic revision

		Follow up 2 weeks-9years	necrosis					GER rate of 11% was low . Authors feel GER was missed in some cases and advocate aggressive diagnosis and treatment of GER to reduce incidence Stricture rates. Due to high complication rate associated with colonic interposition authors advocate preserving the native esophagus as primary conduit where possible If infants with life threatening major congenital anomalies are excluded survival rate exceeding 90% can be achieved

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Congenital Esophageal Stenosis (CES) Diagnosis/Symptoms/Treatment Results	Conclusion
Newman et al (32) 1997	Retrospective Review 1968-1994 26 year period	225 EA patients 61 with esophageal narrowing beyond newborn period 43 had anastomotic stricture (AS) 29M 14 F 18 had CES 10M 8 F 15/18 had Type C EA 3/18 had Type E EA Follow up mean 6.3 years (1.5 -17) **Methodology** Outcomes in Anastomotic strictures compared with CES P<.01 considered significant	**CES** **Location** Distal to anastomosis above GE junction **Diagnosis** 4/18 diagnosis made at time of TEF repair (inability to pass 8Fr NG tube down + inspection) 4/18 narrowing seen in contrast swallow 1 week post repair 9/18 had delayed diagnosis (2weeks-9 months) and in 1 at 6 years CES missed >1 contrast swallows 14 instances **Location** Distal to anastomosis above GE junction Higher incidence of post-operative anastomotic leaks in CES (33%) vs 19% in those with AS (p=NS+ 17/18 had endoscopy No inflammatory changes seen apart from mild ones with impacted foreign body **Symptoms** Seen in 17/18 Feeding difficulty 8/18 especially with solids Recurrent aspiration pneumonia 3/18 Impacted foreign bodies in 10/18 (56%) Between 1-7 times/patient Similar symptoms seen in Anastomotic stricture group 19/43 (44%) had foreign body impactions at anastomotic site **Table 1 compares CES with AS in children with EA** **GER** 16.5% in CES 63% with AS **Fluoroscopy** CES was longer (0.7-3cm) Esophageal diameter was ¼ to ½ of diameter of esophagus above or below CES Diameter increased with age and dilatations **Dilatations** Done in both groups 89% CES 75% AS	Overall incidence of 8% CES in EA-TEF Missed diagnosis of CES is common and can be due to: Being missed during EA repair Lack of dynamic fluoroscopic observation Incomplete esophageal distension Misinterpretation of abnormality as spasm or dysmotility Tube esophagogram useful to distend esophagus adequately None of CES had significant GER, esophagitis or hiatal hernia Foreign body impaction was seen in both groups Most CES patients responded to dilatations Surgery was need only in 2 CES and 3 AS Significantly increased incidence of perforation post dilatation in CES. Majority were with bougie dilatation but as similar dilatations in AS cases did not result in perforation it is likely that the longer length of the stenosis and transmural abnormality of the esophageal wall increase the risk for perforation compared to AS who have only focal fibrosis

			Complications 6/18 (33%) had perforation in CES 0 in AS 5 perforations with rigid bougie 1 with balloon dilatation Mean age of perforation 9 months (1week-1.5years) No apparent difference in location, length of stenosis comparing those who perforated to those who did not 2/6 managed medically 4/6 required surgery **Surgery** 2/18 required surgical resection in CES Histology was FMH 3 AS had surgical resection No histology No deaths or serious long term consequences	

Table 1 Comparison of children with tracheoesophageal fistula *(TEF)* and congenital esophageal stenosis *(CES)* versus anastomotic strictures

	TEF/CES	TEF/anastomotic stricture	Chi-squared test
Number	18/225 (8%)	43/225 (19%)	
Gender	8 F (44%) 10 M (56%)	14 F (33%) 29 M (67%)	
Mediastinal leak	6/18 (33%)	8/43 (19%)	NS
Location	Mid-esophagus to distal esophagus	Proximal at anastomotic site	
Length	Longer than 0.7–3 cm	Very focal	
Foreign body impactions	10/18 (56%)	19/43 (44%)	NS
Esophageal dilatations	7/18 (89%)	32/43 (75%)	
Dilatation perforation	6/18 (33%)	0	$P < 0.001$
Resection of stenosis	2/18 (11%)	3/43 (7%)	

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Results of Balloon dilatation od esophageal strictures	Conclusion
Ko et al (33) 2006	Retrospective review 1999-2003	29 EA patients 19M 10F EA Type All were Type C EA All had primary anastomosis **Methodology** **Indications for dilatation:** Excessive drooling unrelated to oral intake Regurgitation Regression of tolerance of food caliber Discomfort (chest pain) with feeds All had Barium swallow: To confirm stricture Identify location and severity Only strictures >50% of esophageal lumen were dilated GER was looked for GER was treated if detected Dilatation done by interventional radiologists First dilatation done with 8mm balloon Contrast study done post dilatation Patients fed 2hours post dilatation All patients had contrast study 1 month and 1 year post balloon dilatation and every year thereafter to verify status of stricture **Outcome Parameters:** Number of dilatations **Procedural success rates** Stenosis of <30% post dilatation **Primary clinical success** Absence of dysphagia for at least 1 year and weight appropriate to patient's age after initial balloon dilatation **Secondary clinical success** Absence of dysphagia for at least 1 year and weight appropriate to the patient's age after 1 or more dilatation sessions End point of treatment was clinical success	Mean age at dilatation 7.5months (1-26) Mean interval between EA repair and dilatation 6.3months (1-24) 44 balloon dilatations in 29 patients Mean 1.6 (1-5)/patient 18 had 1 8 had 2 2 had 3 1 had 5 dilatations Total inflation time 1-1.5minutes Procedural success rate 93% (27/29) During mean follow up period 3.1 yrs (1-12) none who had procedural and clinical success had recurrent symptoms Follow up contrast study showed normal esophageal lumen or mild narrowing in all Clinical success not achieved in 2 1 had placement of covered retrievable expandable metallic stent with good weight gain Stent retrieved after 3months 1 patient had perforation and TEF as complication of dilatation and had surgery **Complications:** 3 perforations (10%) 2 treated conservatively No mortalities	Balloon dilatation is an effective and safe procedure in anastomotic strictures in EA patients with excellent long term results with a secondary long term success rate of 93% Homogeneity of population as all were Type C EA

STRICTURE in EA-TEF

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of Patients
Patient Characteristics
Methodology</th><th>Anastomotic Strictures
Endoscopic dilatation of strictures</th><th>Conclusion</th></tr>
<tr>
<td>Benjamin et al (34)
1993</td>
<td>Retrospective Review
1981-1986</td>
<td>51 EA patients
27M 24F
Mean BW 2400g (500-4500)

EA Types
Type B 1
Type C 48
Type D 2

Associated anomalies 59%
GI 6

13 died

8 had esophageal replacement

30 had primary repair
15 developed stricture
15 had no stricture

Post operative contrast study done 6wks-6mths depending on symptoms

Stricture defined on basis of swallowing difficulty and confirmed with contrast study
If contrast study showed stricture patient had endoscopy

Esophagoscopy was performed through a wide diameter, round lumen, open tube rigid esophagoscope of suitable diameter and length and bright distal lighting
Antegrade endoscopic Dilatation done under direct vision using graduated dilators
Initially adult Jackson dilators were used
Subsequently pediatric Jackson-Benjamin dilators were used
Esophagoscopy and dilatation was repeated until esophageal lumen improved and patient had lasting symptomatic relief

Symptoms:
Dysphagia 13/15
Food impaction 1
Coin obstruction 1</td>
<td>15/30 (50%) developed anastomotic strictures

68 endoscopic dilatations on 15 patients
Mean number of dilatations 4.5 (1-12)

Time from EA repair to first dilatation mean 7.5months (1-35)
75% of patients presented by 6months or sooner

All patients became asymptomatic

Complication:
1 perforation treated conservatively

No significant difference in gap length between patients with and without strictures

<table>
<tr><th></th><th>Gap cm</th><th>No of Children</th></tr>
<tr><td>Stricture Group N=15</td><td><0.5
0.5-2
>2
Unspecified</td><td>3
4
4
4</td></tr>
<tr><td>No Stricture N=16</td><td><0.5
0.5-2
>2
Unspecified</td><td>3
5
5
2</td></tr>
</table>

8 had anastomotic leak
4 developed strictures, 4 did not

6 had recurrent TEF
2/6 developed strictures
Both had severe GER

GER
Diagnosed by vomiting/contrast study and in most cases pH Metry and/r milk scan
GER in 2/15 of non stricture group
GER seen in 8/15 of stricture group
3/8 had fundoplication

10/15 had tracheomalacia on bronchoscopy
No association between stricture formation and tracheomalacia</td>
<td>Esophagoscopy and direct vision antegrade bouginage of anastomotic strictures in EA patients is relatively safe and effective

Stricture formation not related to gap size unlike other studies.

Dimension of stricture on endoscopy did not correlate with the appearance on contrast study. Swallowing difficulty was a better indicator of stricture severity

Normal initial post operative contrast study does not preclude later development of strictures (1 patient presented at 35 months)
Delayed onset could be due to GER

Early endoscopic inspection and treatment of stricture is important as it is easier to treat when less firm and fibrotic

Number of dilatations depends on swallowing difficulty, size of esophageal lumen and success achieved with each dilatation

Patients with stricture had higher incidence of GER
However insufficient number of patients to draw conclusion about effect of fundoplication on management of stricture</td>
</tr>
</table>

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Results of Mitomycin C application	Results of dilatation of strictures (Control Group)	Conclusion
Chapuy et al (35) 2013	Retrospective review (case cohort) and prospective	134 EA patients 46/134 had esophageal strictures 25/46 responded to 1-2 dilatations and were excluded from study 21 had at least 3 dilatations From 2007 to 2013 ,11 patients who had at least 3 dilatations received topical Mitomycin C 10/21 cases dilated before 2007 had dilatations alone **MitomycinC Group** 8 had Type C EA 3 had Tupe A EA Symptoms of regurgitation/cough with feeds/solid food impactions at median age 4months (1-13) Barium swallow in all Strictures < 2mm in length Mean luminal opening 2.1mm (1-4) **Control Group** 8 had Type C EA 1 Type D EA 1 Type A EA with long gap Symptoms Regurgitations/cough with meal/solid food impactions before median age cof 6 months (1-70), p=NS Strictures <2mm in length Mean luminal opening 1-4mm **Methodology** Recurrent anastomotic strictures defined as those who had 3 esophageal dilatations From 2007 all patients who had at least 3 dilatations received 1 or more topical application of Mitomycin C at the time of the endoscopic dilatation compared to a historical cohort from before 2007 of children who had at least 3 dilatations for anastomotic strictures Endoscopic dilatation done under GE 2 minutes/dilatation Mitomycin C 0.1mg/ml solution, max 2-3ml used per session Topically applied for 2 minutes Dysphagia symptoms evaluated through	First endoscopic dilatation done at median age of 8 months (1-87) First Mitomycin C application median age 11 months (3-183) 5 had 1 application of Mitomycin C 5 had 2 applications 1 had 6 applications 11 patients had median 5 dilatations All were on PPI (Lansoprazole 1-2mg/kg/day) Median follow up 51 months (20-73) 3/11 needed >3 dilatations 2/11 mild dysphagia persisted after 3 dilatations, but endoscopy showed resolution of stricture 1 has been symptom free for 55 months 5/11 needed median of 7 (4-11) dilatations for resolution of stricture Despite Mitomycin C and 7 dilatations 1 with Type A EA had refractory stricture and needed surgery at 15 months At end of follow up 2 needed 4th or 6th dilatation **Complications** No short term side effects 8/11 had endoscopy and biopsy and showed no dysplasia 1 had recurrent TEF at 10 months	First endoscopic dilatation median age 10 months (2-77), p=NS 10 patients had median of 3 dilatations Endoscopic or radiological control done at median time of 98 months (3-208) after last dilatation confirmed absence of dilatation in 9/10 patients 5 had mild dysphagia or food impactions 1 had no symptoms 62 months after last dilatation	First to compare outcome of patients treated with or without Mitomycin C First study to look at only effect of Mitomycin C in Strictures in EA patients 2 groups comparable in terms of number of patients, Type of EA, clinical symptoms, anastomotic strictures and surgery Cannot conclude that group who received adjuvant Mitomycin C had a better outcome compared to control group who received endoscopic dilatations alone Concentration of Mitomycin C could have influenced outcome but most studies have used same concentration No short term side effects of Mitomycin C reported but recurrent TEF could have been due to it 8/11 with biopsies no dysplasia seen but long term follow up is warranted due to risk of malignancy especially in EA patients who already have increased risk of esophageal carcinoma Type of EA, tension at anastomotic site, length of stricture, GER are factors that may potentially affect effect of Mitomycin C Historical control had longer follow up Efficacy of Mitomycin C application in preventing recurrence of esophageal anastomotic strictures with repaired EA is yet to be proven Long term safety of Mitomycin C application needs to be evaluated with serial biopsies

		a questionnaire End point was to compare resolution of stricture as assessed by xray and endoscopy between Mitomycin C group and the group that received dilatations alone			

STRICTURE in EA-TEF

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of Patients
Patient Characteristics
Methodology</th><th>Anastomotic Complications</th><th>Symptoms</th><th>Conclusion</th></tr>
<tr>
<td>Lilja et al (36)
2008</td>
<td>Retrospective Review
1986=2005</td>
<td>Patients from 1986-1995 compared to those from 1996-2005

147 EA patients

EA Types

1986-1995
Type A 6 (7.3%)
Type B 2 (2.4%)
Type C 69 (84.1%)
Type D 0
Type E 5 (6.1%)

1996-2005
Type A 3 (4.6%)
Type B 0
Type C 57 (87.6%)
Type D 0
Type E 5 (7.7%)

Demographics

1986-1995
50M 32 F
Mean gestation 38.5wks (29-42)
Mean BW 2750g (1386-4320)
Major cardiac defects 19 (23%)
VACTERL 15 (18%)
VLBW 2 (2%)
Overall survival 87%

1996-2005
35M 30 F
Mean gestation 38wks (25-42)
Mean BW 2699g (525-4020)
Major cardiac defects 19 (29%)
VACTERL 13 (20%)
VLBW 5 (8%)
Overall survival 94%

Spitz Classification
1986-1995
n=82
Group I 58/62 (93.5%)
Group II 13/19 (68.4%)
Group III 0/1 (0%)

1996-2005
n= 65
Group I 44/44 (100%)
Group II 14/18 (77.8%)
Group III 3/3 (100%)</td>
<td>1986-1995
Anastomotic stricture 53
Anastomotic Leak 7
Recurrent TEF 10

1996-2005
Anastomotic stricture 59, p+NS
Anastomotic Leak 6
Recurrent TEF 5

Strictures were all treated by balloon by dilatation
Mean number of dilatations 4 (1-30)</td>
<td>
<table>
<tr><th></th><th>1-5 yrs (%)</th><th>6-10 yrs (5)</th><th>11-15 yrs (%)</th><th>16-20 yrs (%)</th></tr>
<tr><td>Dysphagia</td><td>65</td><td>55</td><td>64</td><td>60</td></tr>
<tr><td>GER</td><td>38</td><td>40</td><td>44</td><td>43</td></tr>
<tr><td>Omeprazole</td><td>27</td><td>30</td><td>20</td><td>6</td></tr>
<tr><td>Coughing</td><td>43</td><td>33</td><td>32</td><td>36</td></tr>
<tr><td>Chest Infections</td><td>11</td><td>25</td><td>56</td><td>40</td></tr>
<tr><td>Impaired Exercise Capacity</td><td>27</td><td>18</td><td>32</td><td>20</td></tr>
<tr><td>Shortness Of Breath</td><td>36</td><td>21</td><td>32</td><td>53</td></tr>
<tr><td>Asthma Medications</td><td>35</td><td>40</td><td>56</td><td>36</td></tr>
</table>
Fundoplications 11% in period between 1986-1995 and 9% I the period between 1996-2005
</td>
<td>Incidence of major cardiac defects increased from 23% to 29% but overall survival increased from 87% to 94%

Spitz classification still seems to be valid

The presence of a major cardiac abnormality was a stronger predictor of survival than prematurity and indicates improvement in neonatal care and nutritional and ventilator support

Incidence of anastomotic leakage and recurrent fistula did not change over time

Anastomotic stricture rate increased from 53 to 59%

In patients between 16-20years old, 40-50% had gastrointestinal and respiratory symptoms. This could be because only 6% were on PPI and low fundoplication rate

Risk factors for strictures include GER, anastomotic tension and leakage. As anastomotic leakage rate was unchanged increase in stricture rate could be due to higher rate of primary anastomosis with mobilization of distal esophagus and displacement tof esophagogastric junction

Gastrointestinal and respiratory symptoms did not improve with age

No esophageal replacement needed in last 10 years

Improved transition to adult services needed</td>
</tr>
</table>

		Surgical Techniques **1986-1995** Primary anastomosis 64 (78%) Gastrostomy 12 (15%) Colon interposition 3 Gastric Interposition 1 Cervical esophagostomy 1 **1996-2005** Primary anastomosis 55 (85%) p=NS Gastrostomy 4 (6%) p=NS Colon interposition 0 Gastric Interposition 0 Cervical esophagostomy 0 **Number of patients interviewed** **Age at interview** 1-5 37 6-10 33 11-15 25 16-20 30 Total 125 **Median age at interview 10 yrs** 88 patients in school age 90% attended normal school 16-20yrs, 21 attended high school 4 university 3 working'2 unemployed		

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Outcomes with use of externally removable stents for EA strictures and esophageal perforations	Conclusion
Manfredi et al (37) 2014	Retrospective Review 2010-2013	24 EA patients 11M Age at time of placement 22months (3mths-12yrs) Weight at time of placement 10.6kg (3.9-55.2) Total stents 41 Number of stents/patient 1.7 (1-7) **Indications for stent placement:** Refractory Stricture 23 Inability to dilate lumen to 10-12mm over 5 sessions at 2 week intervals Post operative anastomotic leak (perforation) 4 Post dilatation esophageal leak (perforation) 10 **Stents used** Self expandable plastic stents (SEPS) 14 Fully covered self expandable metal stents (FCSEMS) 27 Due to patient size airway stents were used in most patients 32 Esophageal stent 9 **Stent Diameter** 8mm 1(2%) 10mm 19 (46%) 12mm 13 (32%) 14mm 6 (15%) 16mm 2 (5%) **Stent Length** 30mm 5 (12%) 40mm 21 (51%) 50mm 5 (12%) 60mm 1 (2%) 70mm 9 (22%) **Duration of stent placement** Refractory strictures 9.7days (2-30) Perforation 9.9days (3-22) Stents placed under endoscopic and fluoroscopic guidance over guide wire Stent placement confirmed by endoscopy and fluoroscopy Serial CXR every 24-48hrs to look for stent migration Hospitalised for duration Those with perforation got antibiotics 3/14 had concomitant chest drain Stent removal done by endoscopy using rat	**Procedural Success** Stricture resolution defined as no additional therapy required after stent removal at >/=30days and at >/=90days For perforation success was defined as closure of the leak at the time of stent removal. This was confirmed by contrast study Patients with post dilatation leak had stent placed at time of leak Those with post anastomotic leak had 1 month conservative treatment prior to stent placement All had successful placement and retrieval of all stents Stricture resolution rate at >/=30days post stent removal 39% (9/23) The 90 day success 26% (6/23) 64% (9/14) had successful closure of perforation post stent therapy Post dilatation perforation the success was 80& (8/10) Post surgical perforation 25% (1/4) In 2 of the post dilatation perforation endoscopic clips placed at time of stent removal **Complications** **SEPS** **FCSEMS** Stent migration 3(21%) 2 (7%) Respiratory Distress 1 (7%) 0 Granulation tissue Overgrowth 0 10 (37%) Stent induced Ulceration 0 6 (22%) Pain and retching 4 (23%) 7 (26%)	High stricture recurrence on stent removal limits usefulness of stents in treating recalcitrant anastomotic strictures in EA patients. 2 outliers had 6/7 stent sessions but finally needed surgery Stent duration and stent type did not correlate with success of treatment Stents have role for treatment of post dilatation perforations 1 week was sufficient in most cases to promote leak closure Careful monitoring with near daily xrays post stent placement to confirm stent location important to reduce adverse events-cost/radiation exposure Both FCSEMS and SEPS placement is technically feasible and had acceptable safety profile but SEPS were more likely to migrate Granulation tissue and ulceration more likely to occur with longer stent duration Stent placement for post anastomotic leaks does not appear to be of benefit Limitations: retrospective, Small sample size But largest study to look at esophageal stents in young children with a homogenous EA population **Most other studies report 12%-80% success rate (Table 6)** but the patient groups were more heterogeneous (mainly caustic) and not confined to EA patients alone

		toothed forceps		

TABLE 6. Stent literature on benign esophageal strictures

Author	Stent type	Sample size	Reported success*	Stricture type
Studies in adult populations				
Repici[24]	SEPS	15	80%	Mixed benign
Dua[20]	SEPS	38	32%	Mixed benign
Barthel[19]	SEPS	8	12%	Anastomotic
Pennathur[23]	SEPS	9	22%	Mixed benign
Fiorini[21]	FCSEMS	10	50%	Mixed benign
Kim[22]	FCSEMS	55	33%	Mixed benign
Bakken[18]	FCSEMS	10	20%	Mixed benign
Studies in pediatric populations				
Broto[16]	SEPS	10	50%	Caustic
Zhang[17]	FCSEMS	8	75%	Caustic
Best[4]	FCSEMS	7	86%	Mixed benign

SEPS, Self-expandable plastic stent; *FCSEMS,* fully covered self-expandable metal stent.
*Reported success defined as no recurrent stricture.

STRICTURE in EA-TEF

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of Patients
Patient Characteristics
Methodology</th><th>Anastomotic complications and their treatment</th><th>Long term outcomes
Present Condition
Deaths</th><th>Conclusion</th></tr>
<tr>
<td>Sillen at al (38)
1988</td>
<td>Retrospective review
1967-1984</td>
<td>110 EA patients
60 (55%) Male
50 (45%)Female
BW >2500g 77 (70%)
2000-2500g 19 (17%)
<2000g 14 (13%)

48 (44%) had associated anomalies

EA Types
Type A 7 (6%)
Type B 1 (1%)
Type C 100 (91%)
Type D 1 (1%)
Type E 1 (1%)

Patients divided into 2 groups

No or Moderate gap </=2cm 94
Long gap >2cms 16

<table>
<tr><th>Mode of treatment</th><th></=2cm</th><th>>2cms</th></tr>
<tr><td>Primary anastomosis</td><td>90</td><td>11</td></tr>
<tr><td>Division of TEF + gastrostomy</td><td>4</td><td>0</td></tr>
<tr><td>Delayed anastomosis</td><td>0</td><td>2</td></tr>
<tr><td>Primary transplantation</td><td>0</td><td>2</td></tr>
<tr><td>Delayed tranasplantation</td><td>0</td><td>1</td></tr>
<tr><td>Total</td><td>94</td><td>16</td></tr>
</table>
</td>
<td>Leakage confirmed by hydro pneumothorax in xray and by contrast study

Stricture defined as need for 3 or more consecutive dilatations done for swallowing difficulty and just based on result of contrast study
Dilatation done with bougies
Surgery done if restructuring occurs

GER diagnosed by xray and endoscopy
Nissen Fundoplication done for aspiration pneumonitis, poor feeding and failure to thrive, esophagitis

Complications in 39 (43%)

<table>
<tr><th>Complication</th><th></=2cm n=90</th><th>>2cm n=13</th></tr>
<tr><td>Anastomotic Leak</td><td>24 (26%)</td><td>13 (100%)</td></tr>
<tr><td>Anastomotic Stricture</td><td>16 (18%)</td><td>9 (70%)</td></tr>
<tr><td>GER</td><td>5 (5%)</td><td>5 (38%)</td></tr>
</table>

Treatment of complications

<table>
<tr><th>Treatment</th><th></=2cm n=90</th><th>>2cms n=13</th></tr>
<tr><td>Anastomotic Leakage</td><td></td><td></td></tr>
<tr><td>Drainage</td><td>19</td><td>9</td></tr>
<tr><td>Drainage + Resuture</td><td>5</td><td>4</td></tr>
<tr><td>Anastomotic Stricture</td><td></td><td></td></tr>
<tr><td>Bouginage</td><td>13</td><td>8</td></tr>
<tr><td>Bouginage + Reoperation</td><td>3</td><td>1</td></tr>
<tr><td>GER</td><td></td><td></td></tr>
<tr><td>Conservative</td><td>2</td><td>2</td></tr>
<tr><td>Conservative + Fundoplication</td><td>3</td><td>3</td></tr>
</table>

Drainage for anastomotic leakage
16+/-2days non long gap group
21+/-4days in long gap group</td>
<td>Non long gap group
74/94 (80%) no major problems
None of surviving 74 patients has major problems but minor swallowing issues and arrest of ingested foreign body seen. This is due to dysmotility not stricture

Long gap group
10/13 (77%) are alive
9/10 have no major problems
1 who need 100 dilatations over 4 years, stricture resection and 2 fundoplication still has swallowing problems

Causes of death in relation to gap length

<table>
<tr><th>Causes Of Death</th><th></=2cms n=94</th><th>>2cms n=16</th></tr>
<tr><td>EA</td><td></td><td></td></tr>
<tr><td>Preoperative Complication</td><td>3 (3%)</td><td>-</td></tr>
<tr><td>Anastomotic Complication</td><td>2 (2%)</td><td>2 (12%)</td></tr>
<tr><td>Others</td><td>2 (2%)</td><td>1 (6%)</td></tr>
<tr><td>Associated Anomalies</td><td>13 (14%)</td><td>1 (6%)</td></tr>
<tr><td>Total</td><td>20 (21%)</td><td>4 (24%)</td></tr>
</table>

Causes of death in relation to time period

<table>
<tr><th>Causes Of Death</th><th>1969-1976 n=57</th><th>1977-1984 n=53</th></tr>
<tr><td>EA</td><td></td><td></td></tr>
<tr><td>Preoperative Complication</td><td>2 (4%)</td><td>1 (2%)</td></tr>
<tr><td>Anastomotic Complication</td><td>4 (7%)</td><td>-</td></tr>
<tr><td>Others</td><td>3 (5%)</td><td>-</td></tr>
<tr><td>Associated Anomaly</td><td>10 (18%)</td><td>4 (7%)</td></tr>
<tr><td>Total</td><td>19 (34%)</td><td>5 (9%)</td></tr>
</table>
</td>
<td>Satisfactory long term results in infants with non long gap EA with normal swallowing function after a few years

Survival rate is close to 100% and is related to more associated anomalies and not BW or pneumonia due to modern anesthesia and intensive care

Long gap atresia causes relatively high morbidity with swallowing problems for several years</td>
</tr>
</table>

			Dilatation for stricture Bouginage 6+/-1 in non long gap group 19+/-10 (3-98) dilatations in long gap group over 1 month to 4 years		

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	GER	Fundoplication	Conclusion
Corbally et al (39) 1992	Retrospective Review 1975-1989	153 EA Patients 55 had GER 12 had Nissen Fundoplication 10/12 had Type C EA 2/12 had Type A EA and had delayed anastomosis 2 had Livaditis myotomy Mean follow up 57.8 months (5-154) Tracheomalacia seen in 3	55 (40%) had GER Manometry/pH Metry not routinely done GER diagnosed on contrast study and symptoms Endoscopy showed esophagitis in 5	12/153 (8%) had fundoplication **Indications:** Stricture 8/12 (67%) , 5/8 had multiple dilatations prior to fundoplication Vomiting 11/12 (92%) Failure to thrive 100%, all were less than 3rd centile for weight Respiratory infection 11/12 (92%) Aspiration pneumonia 8/12 (67%) Complications of fundoplication: Wound infection 1 Splenectomy 1 Death 1 Outcome of Fundoplication: Radiological reflux seen in 3/12 Dysphagia in 3/12 and 1 patient is tube fed Recurrent vomiting in 3/12 Recurrent respiratory infections in 4/12 Adequate weight gain with weight on 50th centile in 8/12	No comparison of outcomes done between those patients with GER who had fundoplication and those who did not 25% incidence of recurrent reflux, based on recurrence of vomiting. Recurrent chest infection can also be an indication of failure of fundoplication and was seen in 33% post fundoplication Poor weight gain persisted in 33% post fundoplication Significant dysphagia was seen in 25% post fundoplication Hence careful patient selection is important as most cases of GER in EA patients can be managed conservatively. However persistent anastomotic stricture, near fatal respiratory events and frequent respiratory infections indicate the need for surgery. Low fundoplication rate in this study and more aggressive treatment of reflux might have been needed in some especially the 5/8 patients with strictures who needed >5 dilatations prior to fundoplication Continued long term surveillance is needed post fundoplication in EA patients because of the increased incidence of complications and reflux recurrence

STRICTURE in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Anastomotic Complications	Dysphagia	Quality of Life	Conclusion
Gatzinsky et al (40) 2011	Case cohort study 1968-1983	79 consecutive EA survivors Questionnaire on dysphagia, GER and QOL sent out 73/79 (92.4%) returned questionnaire 34F 39M The 6 who did not respond also had Type C There was no significant difference in sex, age, type of EA from responders and non responders Mean age32yrs (25-40) Mean weight of women 65kg (43-130) Mean height of women 165cm (158-173) Mean weight of mean 77.5kg (58-120) Mean height of men 178cm (164-190) Mean BMI of group 24 (17.6-50.8) In order to make study homogenous 63 patients with Type C EA chosen 22 had physician diagnosed asthma 3 had mental disorders 2 had IBD 1 had pace maker 1 had hepatitis 1 gout 28 (35%) had associated malformation Mean BW 2901g (1510-4300) Questionnaires chosen: Numerical Dysphagia score 9 items of food listed with different viscosities and solidities. Score of 45 means severe dysphagia GerdQ (assessing GER) 6 item questionnaire Questions on heartburn and regurgitation used for calculations as they correlate well with GER	Anastomotic stricture defined as need for 3 or more dilatations Strictures dilated by bouginage 79 patients Strictures 16 in Type C Strictures 3 in Type A Recurrent TEF 2 in Type C only Anastomotic leak 7 in Type C, 2 in Type A and 1 in Type B Reoperation for stricture/leakage or refistulisation 11 in Type C and 1 in Type A 5 had GER requiring fundoplication	27/63 had no dysphagia 36 (57%) had varying swallowing difficulties Higher viscosity and solidity of food led to more dysphagia Scoring of those with symptoms was 12.2 (mean; SD 7.7) and 11.5 (median; 3.5-36) When comparing patients with and without dysphagia with respect to smoking, height, weight, BMI, sex, anastomotic tension, strictures needing >3 dilatations, need for reoperation, cardiac anomalies, VACTERL or fundoplication there was no significant difference between the two groups However when looking at type of EA the Dysphagia Score in the 63 Type C EA was 6.98 (mean; SD 8.63) vs 24.7 (mean; SD 5SD) in the 3 with Type A EA, p=.006 Although Fundoplication made no difference, 20 (32%) reported heartburn and 25 (40%) had regurgitation. When comparing dysphagia scores to heartburn no correlation was seen but logistic regression showed strong correlation between dysphagia score and regurgitation yielding OR of 2.8	There was no difference in QOL between Type C EA and the control group neither with regard to the 8 components of health, nor in their overall physical and mental health No correlation between QOL and dysphagia score	Prevalence of heartburn and regurgitation in the cohort using the questionnaire was32% and 40% respectively, although absence of symptoms does not preclude the presence of GER in EA patients Strong correlation between dysphagia and regurgitation. This could be because dysmotility facilitates both dysphagia and regurgitation or that dysphagia can be exacerbated by regurgitation. Authors plan to look at actual incidence of GER with pH Metry in future. Patients with pure EA had more dysphagia than those with distal fistula, but there were only 3 pure EA patients Dysphagia to some extent seen in 57% of those with distal fistula Overall quality of life was good and did not differ from reference group. No difference in overall physical or mental health. There was no correlation between QOL and presence or absence of dysphagia No correlation between the different SF-36 item scores and the dysphagia score This could be cause EA patients with dysphagia might have become accustomed to their swallowing difficulties and consider them to be part of their lives Dysphagia numerical score has advantages when it comes to evaluating the possible influence of dysphagia. A standardized definition of dysphagia and Dysphagia would make comparisons and recommendations for follow up easier

		SF-36v2 (validated for QOL) 8 components for health and 2 components for physical and mental health For comparison age and sex matched reference sample randomly selected from Swedish SF-36v2 population database				

STRICTURE in EA-TEF

<table>
<tr><th>Author/Year</th><th>Study Type</th><th>Number of Patients
Patient Characteristics
Methodology</th><th>Anastomotic Complications</th><th>Stricture</th><th>Mortality</th><th>Conclusion</th></tr>
<tr>
<td>Chang et al (41)
2012</td>
<td>Retrospective Review
1995-2010</td>
<td>107 EA Patients
35 were excluded

72EA patients analyzed
42M 30F
Gestational age 38+/-2.7weeks
>/=37 53 (73.6)
<37 19 (26.4)
BW 2.6+/-0.6kg
>/=2.5 46(63.9)
1.5-2.5 22 (30.5)
<1.5 4 (5.6)
Combined anomalies 50 (69.4%)

Types of EA
Type A 11 (15.3%)
Type C 59 (81.9%)
Type E 2 (2.8%)

In 17 cases (23.6%) CT scan was done to evaluate anatomy of TEF and measure gap distance

Surgery
Type C (59)
Primary repair 52, staged 7
Type A (11)
All had staged repair
Type E (2)
Both had primary repair

Follow up 42+/-44months

Patients were grouped into two time periods:
Early Period 1995-2003
Late Period 2004-2010</td>
<td>53 (73.6%) had post operative complications

<table>
<tr><th>Complications</th><th>N (%)</th><th>Number needing operations</th></tr>
<tr><td>Anastomotic Leakage</td><td>17 (23.6%)</td><td>7 (9.7%)</td></tr>
<tr><td>Recurrent TEF</td><td>6 (8.3%)</td><td>6 (8.3%)</td></tr>
<tr><td>Pneumonia</td><td>10 (13.9%)</td><td>0</td></tr>
<tr><td>GER</td><td>3 (4.2%)</td><td>0</td></tr>
<tr><td>Hiatal Hernia</td><td>2 (2.8%)</td><td>0</td></tr>
<tr><td>Tracheomalacia</td><td>7 (9.7%)</td><td>2 (2.8%)</td></tr>
<tr><td>Sub Glottic Stenosis</td><td>2 (2.8%)</td><td>2 (2.8%)</td></tr>
<tr><td>Others</td><td>8 (11.1%)</td><td>0</td></tr>
<tr><td>Total</td><td>53 (73.6%)</td><td>14 (19.4%)</td></tr>
<tr><td></td><td></td><td></td></tr>
</table>

Anastomotic leakage was the second most commonest complication
6/7 leakage patients who needed surgery were found to have recurrent TEF
Mean age of TEF recurrence was 6.7months (0.6-23)

Comparison of outcomes between two study periods
<table>
<tr><th>Outcome</th><th>Total N=72</th><th>Early Period N=33</th><th>Late Period N=39</th><th>P value</th></tr>
<tr><td>Complication</td><td>53 (73.6%)</td><td>26 (78.8%)</td><td>27 (69.2%)</td><td>0.517</td></tr>
<tr><td>Anastomotic Leakage</td><td>17 (23.6%)</td><td>13 (39.4%)</td><td>4 (10.3%)</td><td>0.009</td></tr>
<tr><td>TEF Recurrence</td><td>6 (8.3%)</td><td>5 (15.2%)</td><td>1 (2.6%)</td><td>0.087</td></tr>
</table>
</td>
<td>Strictures were the most common complication.31 (43.1%)
Strictures treated with bouginage or balloon dilatation
3 (4.2%) needed surgical resection

Comparison of strictures between two study periods showed 11 (33.3%) in Early Period and 20 (51.3%) in Late Period, p=0.196

Relationship between stricture and esophageal gap and circular myotomy
<table>
<tr><th>Complication</th><th>N</th><th>Stricture (%)</th><th>P value</th></tr>
<tr><td>Esophageal Gap</td><td>49</td><td></td><td>0.042</td></tr>
<tr><td>Short <3cm or 3VB</td><td>20</td><td></td><td></td></tr>
<tr><td>Long >3cm or 3VB</td><td>29</td><td></td><td></td></tr>
<tr><td>Circular Myotomy</td><td>51</td><td></td><td>0.078</td></tr>
<tr><td>None</td><td>33</td><td></td><td></td></tr>
<tr><td>Done</td><td>18</td><td></td><td></td></tr>
</table>
</td>
<td>Overall mortality was 11 (15.3%)

Mortality rate of patients with a BW <2.5kg 9/26 (34.6%) was significantly higher than that of patients weighing at least 2.5kg 2/46 (4.3%), p=.001

Comparison of mortality outcomes between two study periods showed that in Early Period it was 9 (27.3%) vs Late Period 2 (5.1%), p=0.023</td>
<td>High incidence (73.6%) complications in EA patients

Post operative strictures were significantly correlated with gap length

Patients weighing less than 2.5kg had a significantly higher mortality rate

Relatively high incidence of Type A EA (15.3%) However 2/3 patients who were repaired using esophago-colo-gastrostomy (ECG) died compared to those who were repaired using transhiatal gastric pull up (THGP) or transthoracic esophago-esophagostomy after elongation (TEEE) therefore authors recommend TEEE or THGP for Type A EA.

Although chest CT was used to define anatomy and assess gap length in 23.6% of cases results did not confirm effectiveness of 3D reconstructed image for this

GER developed in only 4.2% and all were treated conservatively. But GER might have been underestimated due to retrospective nature of study and insufficient follow up period

Survival of EA patients has improved over years and rate of anastomotic leakage has decreased, but there is still a high overall morbidity</td>
</tr>
</table>

Study **Author/year**	**Type of Study**	**Number of patients**	**Patient characteristics**	**Method**	**Results** **Auerbach Plexus**	**Conclusion** **Additional remarks**
Nakazato et al 1986	Retrospective review Case control	5 EA-TEF patients 9 controls without gastrointestinal disease	All cases chosen from autopsy files 5 EA-TEF 4 had no repair of the EA-TEF 1 had only ligation of TEF 2M, 3F Conceptual age (gestational age + postnatal age) 28weeks-40weeks 2 had gastrostomy 1 had repair of left diaghragmatic hernia	Specimen taken from proximal and distal esophagus and fundus of stomach, fixed in formal and taken for micro dissection , histological examination and point-count morphometry of Auerbach Plexus	Relative fraction of neural tissue in Auerbach plexus is significantly higher in the distal compared to proximal esophagus in control patients. But in EA-TEF patients this is revered and the distal esophagus is more deficient in Auerbach plexus compared to proximal esophagus. All 5 patients showed thinner than normal inter-ganglionic fibres in a looser network than normal with larger ganglia in the Auerbach Plexus in the distal esophagus and to a lesser extent in the proximal esophagus compared to controls. The smooth muscle layers were normal. The Auerbach plexus of the gastric fundus of all EA-TEF patients was also abnormal with a looser than normal network with larger ganglia and thicker interganglionic fibres compared to controls.	Abnormal low relative fraction of neural tissue in the Auerbach plexus in EA-TEF infants, with the deficiency relatively greater in the esophagus distal to the interruption compared to the upper segment. Hence dysmotility resulting in dysphagia and GER seen in EA-TEF is secondary to a congenital abnormality in myenteric plexus. Abnormalities of myenteric plexus seen in gastric fundus could result in delayed gastric emptying. Gastrostomy probably not responsible for delay in gastric emptying seen in EA as only 2 patients had gastrostomy in this cohort.

<table>
<tr><th>Study
Author/year</th><th>Type of Study</th><th>Number of patients</th><th>Patient characteristics</th><th>Method</th><th>Results
Morphologic and immunohistochemical findings in EA-TEF</th><th>Conclusion
Additional remarks</th></tr>
<tr>
<td>Zuccarello et al
2009</td>
<td>Case cohort</td>
<td>12 EA-TEF
7 M, 5F

5 Controls</td>
<td>Average gestational age 36.1+/-2.21
Average post natal age 3,25+/-1.95

All Type C, without long gap

Specimens from proximal segment in 9 cases and distal in 10 at time of primary anastomosis

Controls
Specimens obtained at autopsy. Death from unrelated causes. From 1-2mm above carina</td>
<td>Serial sections of (UEP) upper esophageal pouch and (DES) Distal esophageal segment and controls were stained with H&E and an immunohistochemical panel with primary monoclonal and polyclonal antibodies against:

Anti-A (Actin)
Anti S-100
Anti NFs (Neurofilament)
Anti-P (Peripherin)
Anti-NSE (Neuron Specific Enolase)
Anti CgA (Chromogranin A)</td>
<td>
<table>
<tr><th>Tissue</th><th>UEP</th><th>DES</th></tr>
<tr><td>Mucosa</td><td>Epithelial Hyperplasia

Dysplasia and Dystrophy

Reduction of Muscularis mucosae</td><td>Epithelial Hyperplasia

Dysplasia and Dystrophy

Absence of Muscularis mucosae</td></tr>
<tr><td>Submucosa</td><td>Hyperplasia Of elastic fibers

Infiltration of myofibrilles

Dysplasia And dystrophy</td><td>Hypoplasia Of elastic fibers

Dysplasia And dystrophy</td></tr>
<tr><td>Circular Musculature</td><td>Muscular Hypoplasia

Fragmentation Of myofibrilles</td><td>Muscular Hypoplasia

disorganization Of myofibrilles</td></tr>
<tr><td>Intermuscular Collagen And Elastic tissue</td><td>Connective Fibrosis

Endomysial Fibrillogenesis</td><td>Connective Fibrosis

Endomysial Fibrillogenesis</td></tr>
<tr><td>Auerbach Plexus</td><td>Reduction of Neurocells

Increase of Schwann’s cells

Immaturity of neurocells</td><td>Reduction of Neurocells

Increase of Schwann’s cells

Immaturity of neurocells</td></tr>
<tr><td>Longitudinal Musculature</td><td>Muscular Hypoplasia

Fragmentation Of myofibrilles</td><td>Muscular Hypoplasia

Disorganization Of myofibrilles</td></tr>
</table>

In Controls the distribution of the neural elements was homogenous at both levels of the esophagus
</td>
<td>EA-TEF patients showed quantitative and qualitative differences with sparser nervous tissue in the DES compared to UEP and when compared to controls.

Defective NF staining and increased P immunostaing n EA-TEF means defective or absent maturation of nerve cells, with increase in immature neuroblasts. The reduced CgA reactivity signifies defective neurotransmitter release.

Congenital histomorphological alterations in muscular and nervous elements, with delay in neuronal differentiation and myenteric plexus organization contribute to dysmotility resulting in dysphagia and GER in EA-TEF</td>
</tr>
</table>

Study **Author/year**	**Type of Study**	**Number of patients**	**Patient characteristics**	**Method**	**Results** **Morphologic and immunohistochemical findings in EA-TEF**	**Conclusion** **Additional remarks**
Boleken et al 2007	Case cohort	9 EA-TEF neonates 9 controls	**EA-TEF** Proximal atresia with distal fistula Distal end of proximal pouch Average gestational age 36.66+/-2.23 Average post natal age 4.55+/-2.96 **Controls** Esophagi from autopsy Sections from 1-2mm above carina Av gestational age 37.77+/-2.33 Average post natal age 25.33+/-14.89	Slides prepared and stained with H & E and with specific antibodies by immunohistochemistry: Neurofilament (NF) Synaptophysin (SY) S100 Glial line derived neurotrophic factor (GDNF)	H & E stain Marked hypoganglionosis and immature ganglion cells in myenteric plexus compared to controls (p<.0001) The mucosa, sub mucosa and muscular layers in Ea-TEF were slightly thickened compared to controls (P=NS) But overall thickness of atretic esophagus was greater than in controls (p=.01) NF immunoreactive fibres were significantly less in the myenteric plexus in EA-TEF compared to controls (p=.001) SY immunoreactive fibers and ganglia in the myenteric plexus in and SY immunoreactive nerve fibers in the muscular layer in EA-TEF were significantly less compared to controls (p=.000) GDNF IR in the ganglia and nerve fibers in EA-TEF in the myenteric plexus was significantly less compared to controls (p=0.000) GDNF IR in squamous epithelium in controls was most intense in the basal layer in controls. This was reversed in EA-TEF S-100 protein immunoreactivite cells were increased in the muscular layer in EA-TEF compared to controls (P=NS).As there was no associated NF or SY; these cells were thought to be Schwann cells. All neuronal IRs had +ve and –ve correlation with esophageal wall thickness in both groups (P=NS)	Expression of neuronal markers and numbers of ganglion cells was significantly reduced in EA-TEF compared to controls in the distal end of the upper pouch. The increase in S100 might be a compensatory mechanism in EA-TEF due to hypertrophied glial tissue to compensate for defective neuronal tissue. GDNF is vital for development of and maintenance of neural tissue. It is a member of TGFbeta superfamily. Formation of the ENS and migration from the neural crest requires GDNF signaling via GDNF family receptor alpha1 and Ret tyrosine kinase. Therefore reduced GDNF (as a trophic/induction factor) results in underdevelopment of intrinsic nerve fibers in EA-TEF Which causes dysmotility resulting in dysphagia and GER The cross sectional area in the atresia group was increased which was different that seen in the Adriamycin treated rat fetuses with EA-TEF The lack of correlation between immunoreactivities and esophageal wall thickness means changes in neuronal density is not due to esophageal wall changes.

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Pederiva et al 2008	Retrospective Case cohort	6 babies with pure EA Control 6 newborns	**EA** 3M, 3F Specimens obtained from proximal and distal segments at time of esophageal replacement Mean age at time of surgery 7+/-3.8months **Control** 6 newborns who died of non esophageal causes Mean gestational age 39+/-1.9weeks	Specimen sections stained with: H & E Immunohistochemistry done with antibodies against: Neurofilament (NF) S-100	Mean muscular surface was significantly larger in EA (both proximal and distal segment) compared to controls (P<.05) Neural area relative muscle surface was not calculated because of age mismatch Raw area of intermuscular plexus (Fibrillar network) was larger and denser in pure EA at both levels with immune stainings in: NF Fibrillar surface NF surface of ganglia NF neurons/ganglia S100 Fibrillar surface S 100 Surface of ganglia S 100 Neurons/ganglia P was significant only for proximal end. The distribution and morphology of ganglia of Auerbach plexus was similar in EA and controls Ganglia were larger in EA Number of neurons/ganglia was similar in both groups .	First study to look at intra mural innervation in pure EA at both ends of atretic esophagus. Fraction of neural elements in the intermuscular plexus in pure EA was larger than controls both for density of fibrillar network and size of ganglia. The neuronal population of ganglia was similar in both groups but the size of neurons was larger in pure EA.Findings were identical for both ends of atretic esophagus These findings are different to those described by other authors looking at EA-TEF. ? due to different mechanisms for neuronal innervation in pure EA This study looked at distal atretic esophagus where as other studies looked at distal fistula which has respiratory component in it. These were babies not neonates hence distending intraluminal pressures (swallowing and aspirating at upper pouch and GER at lower pouch) could have modified neural network. Lack of appropriate age or weight matched control group. This could hve exaggerated apparent increased density of fibrillar network in EA. Variable expression of different neuromediators was not explained, but it was suggested that imbalance between excitatory and inhibitory signaling might result in esophageal dysmotility.

Dysphagia and esophageal function in EA-TEF

STUDY Author/ Year	DESIGN	Number Of subjects	Patient Characteristics	Follow up	Incidence Of Dysphagia	Contrast Study results	pH Metry results	Endoscopy results	Type of Manometry	Results of manometry	Association between dysphagia and manometry result	Association with QOL scores	Additional Remarks
Tomaselli et al, 2003	Prospective Cohort	26 overall Contrast 26 Manometry 12(9F) pH metry 12 (9 F) Endoscopy 15 (10 F)	7-28yrs (mean 15.8)	7-28yrs (mean 15.8)	50% based on questionnaire	31% dilatation above anastomosis 15% pseudo diverticulum	16.7% was abnormal (>4%)	20% mild esophagitis	Stationary Water perfused	Mean LES pr 18.9 +/- 10.7 2/12 (16.7%) had hypotonic LES Short intra-abdominal LES in 2/12 (16.7%) Incomplete relaxation of LES in 1/12 Hypotonic proximal esophageal amplitude in 100% Hypotonic distal esophageal amplitude in 7/12 (58.3%) Abnormal peristalsis 100% Seen in at least 30% 1.Simultaneous 75% 2.Dropped 33.3% 3. Interrupted 8.3%			No biopsies taken No info given on number who had fundoplication except for 1 pt with low LES pressure was post fundo 2 pts with low pressure in LES had esophagitis and abnormal pHmetry Dysmotility in contrast studies not commented upon No comment on strictures/dilatations

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Werlin et al 1982	Prospective cohort	14	7M,7F Mean age 7.5yrs (2-20) 11 had TOF + EA 2 had Fundoplication 1 gastric tube replacement hence excluded 7 had dilatations	7.5yrs (2-20)	36%	Done in 10 100% normal pharynx and UES 100% normal peristalsis in cervical esophagus 100% no peristalsis in proximal half of thoracic esophagus 50% absent peristalsis in distal esophagus	GER if pH fell >2 units for >10s 43% GER episodes seen	None	Stationary Water Perfused	100% absent peristalsis in middle third of esophagus 11/13 (85%) had simultaneous non-peristaltic contraction in esophageal body 46% had normal peristalsis in distal third of esophagus (11/12) 92% normal relaxation of LES No abnormal response to Mecholyl in 2 who had test No difference in mean basal LES pr between GER vs non GERpts			Patients <5yes mildly sedated with IV Diazepam Whole pH study done only for 15-30min pH catheter inserted through central lumen of manometry catheter Stress manouvere for GER (abdominal compression, head down, left lateral) No GER seen in 2pts post fundo

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Deurloo et al 2008	Prospective cohort And Retrospective	25 But 5 excluded for manometry and 4 for pH, 3 because of stricture, 1 due to inability to pass catheter through nose and 1 because of technical failure of manometry machine	Mean 28.8 yrs 16M 9F 2 on PPI which was ceased 2 days before Past dilatations 28%	18-42yrs	48% Dysphagia 33% GOR		Classified using DeMeester scores Normal 81% Minor reflux 5% Pathological reflux 14% Proximal mean 0.2+/- 0.4% Distal mean 1.5+/-2.2%	Endoscopy normal 86% Abnormal 14% As per Savary Miller Normal was normal or grade 1 and abnormal >grade2 Biopsies Normal 52% Abnormal 48% As per Ismael Beigi Normal was normal or mild esophagitis and abnormal moderate esophagitis or worse	Stationary Water perfused	Normal mean UES pressure (30.8+/-15.5mmHg)and relaxation with swallows Ineffective esophageal motility in all as per guidelines of Spechler Retrograde contractions in 35% Low amplitude esophageal body contractions in 20% (<15mmHg) Moderate 50% (15-35mmHg) Normal 30% (>35mmHg) Normal mean LES pressures (13.3+/-7.2mmHg)and relaxation with swallows	Association between dysphagia and disturbed motility (p=0.011)	Association between dysphagia and lower scores on general health perceptions (p=0.026) And Standardised physical component (p=0.013) of the SF 36 And poor physical wellbeing (p=0.047) of the GIQLI No association between complaints of GER and QOL, No association between results of endoscopy and pH measurement and or manometry No association between results of biopsies and pH measurement and or manometry Anastomotic leak or previous stricture did not influence study results	Endoscopy and biopsies were done in previous study in 2003

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Montgomery et al 1995	Prospective cohort	18	2 groups Group 1 had minor respiratory complications before 4yrs Group 2 has severe respiratory complications including aspiration and pneumonia that continued after that age 12M 6F Median age 14yrs Median gestational age 40wks	8-21yrs	50% Dysphagia 50% GER	Done in 15 Dysmotility 100% Mild in 56% and Moderate in 44% in group 1 Mild in 50% and severe in 50% in Group 2 Retention of contrast in dilated proximal esophageal segment higher in group 2 Stricture of varying degrees seen in 33% in group 1 and 66% in group2 Total esophageal function score median of 7 (2-13) in group 1 and 12.5 (6-15) in group 2	Done in 13 RI>5% in 25% in Group 1 And 20% in Group 2 Mean Reflux index 2.4% in Gp1 and 2.2% in Gp 2 Reflux episodes 33.5 Gp 1 and 33 Gp2 Longest episode 3.5Min Gp1 and 7min Gp2		Stationary Water perfused	Dysmotility 100%	Associated between esophageal dysfunction in contrast study (more retention in proximal esophagus) and respiratory complications in group 2		44% had normal spirometry in group1 89% had abnormal spirometry in group 2. (25% obstructive and 75% restrictive) No difference in maximal working capacity and capillary blood gases between groups No relationship between GER and decreased pulmonary function But 3 patients in group had previous fundoplication

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Romeo et al 1987	Prospective cohort	20	12M 8F	Neonatal period Pre repair of EA					Stationary and Rapid Pull Through Dry Swallows Paper speed constant at 1 or 5mm/s for proximal and 1mm/s for distal Recordings for 12-24 hours Recordings of proximal pouch in 16 and distal via gastrostomy in 12	Length of proximal pouch 3-4.8cms UES relaxed and contracted with normal amplitude and duration in a normal temporal relationship with swallows in 88% Incomplete (80%) relaxation in <50% of swallows in 18% Body of proximal pouch showed positive basal tone with motor incoordination Distal pouch length 3.8-4.6cms (with TEF) and 2.5-3cms (pure ES) Basal tone of distal body positive 100% Total incoordination of peristalsis 100% Length of LES 0.8-1.5cms Normal LESP (22-35mmHg) in 83% Low in 17% (8-10mmHg) Complete relaxation of LES in 90% Incomplete relaxation of LES in 10% Gastroesophageal gradient present 100%			Only study looking at esophageal motility pre repair of EA/TEF suggest esophageal dysmotility is congenital but abnormality of LES may have iatrogenic component

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Sistonen et al 2010	Population based case control study	101 cases 588 repaired EA- 296 alive-pts with esophageal replacement (34) and emigrated pts (16)-235-169 replied-first 101 who replied were included 287 matched controls	Controls matched for age/BMI/Gender Mean BMI 24Kg/m2 57M Fundoplication 10%	36 yrs (22-57)	Dysphagia 85% in Ea and 2% in controls (p<0.001) Validated symptom questionnaire for GER 34% in EA and 8% in controls (p<0.001) Both GER and dysphagia were equally common with normal histology/esop hagitis or epithelial metaplasia			Endoscopy abnormal 58% Hiatal hernia 28% Barrett's 8% Anastomotic stricture 8% (dilatation 2) LA-A-4 LA-B-2 LA-C-1 Histological esophagitis (Ismail Beigi) 25% (Mild) 22% (moderate) 3%(Severe) Esophagitis with metaplasia 7% Distal 9% Proximal 4% Prox + Distal 12% Columnar metaplasia without goblet cells 15% (12/15 in distal and both prox and distal in 3) All CDX2 +ve Goblet cells 6%(all distal) All CDX2 and MUC2+ve No dysplasia	Stationary Water perfused	Non propagating peristalsis 80% Normal propagating peristalsis 20% Low ineffective distal wave amplitude in esophageal body 83% Achalasia type low amplitude simultaneous waves 15% Normal LES resting pressure and relaxation with swallows 91% Hypotonic LES 6% Ineffective relaxation of LES 3% Normal UES resting pressure and relaxation 100%	Distal wave amplitude <25mmHg associated with epithelial metaplasia (OR 2.6, p =0.002) Non propagating esophageal peristalsis associated with epithelial metaplasia (OR 2.2, p = 0.014)	Other predictors of epithelial metaplasia by multivariate logistic regression model Stricture requiring early resection (OR 24, p = 0.008) Recurrent TEF (OR 24, p = 0.009) >30yrs (OR 20, p = 0.009) Long gap myotomy (OR 19, p = 0.011) Anastomotic stricture in adulthood (OR 8.6, p = 0.011) Epithelial Metaplasia 72% males and 76% >30yrs	Nuclear CDX@ expression seems to predict presence of undetected intestinal metaplasia which will become evident in follow up biopsies 4 fold higher prevalence of Barrett's in EA compared to general population ? need for surveillance endoscopies in EA pts >30yrs with significant primary operative complications

Dysphagia and esophageal function in EA-TEF

STUDY Author/ Year	DESIGN	Number Of subjects	Patient Characteristics	Follow up	Incidence Of Dysphagia	Contrast Study results	pH Metry results	Endoscopy results	Type of Manometry	Results of manometry	Association between dysphagia and manometry result	Other Association with dysmotility	Additional Remarks
Montgomery et al 1998	Prospective case control study	11 patients 11 healthy controls	Patients 23-40yrs Median 29yrs Controls 21-42yrs Median 26yrs No dysphagia No surgery in pharynx or esophagus	23-40yrs Median 29yrs	Dysphagia 73% GER 45% Hoarseness and/or nocturnal cough 18% Pneumonia 27%	No evidence of direct aspiration			Video-Manometry Solid state catheter 3-5 boluses of 10mls, 60% barium contrast wet and dry swallows	1.UES Resting pressure (mmHg) 65 (52.8-120) NS compared to controls 2.UES residual pressure with wet swallows (mmHg) 0.9 (-9.7-6.4) NS compared to controls 3.UES resting pressure with dry swallows- mmHg 1.5(-13.8-4.7) NS compared to controls 4. Duration of UES relaxation (ms) 685 (327-788) NS compared to controls 5. Pharynx contracture pressure (mmHg) 304 (148-464) NS compared to controls 6. Propagation of the contraction wave from UES to upper esophagus (2cms below UES) in cms/sec 1.6 (1.4-2.2) NS compared to controls 7. Timing between contraction of PCI (beginning of contraction) and the UES relaxation (beginning of relaxation) in ms 327 (228-550) significantly less compared to controls 508 (348-593)	No correlation between dysphagia and lack of coordination of swallowing		Incoordination of swallowing demonstrated for the first time in EA group. This may be a risk factor for direct aspiration and respiratory symptoms

										8. Bolus Transit time from pharynx to upper esophagus in ms was significantly lower 66.5 (54.8-99.5)compared to controls 79.5 (65-87.6) 9. No significant difference in amplitude of pressure wave in upper esophagus 10. Below upper esophagus 100% lack of coordination of peristalsis and absence of peristaltic waves 10. Below upper esophagus 100% lack of coordination of peristalsis and absence of peristaltic waves			

Dysphagia and esophageal function in EA-TEF

STUDY Author/ Year	DESIGN	Number Of subjects	Patient Characteristics	Follow up	Incidence Of Dysphagia	Contrast Study results	pH Metry results	Endoscopy results	Type of Manometry	Results of manometry	Association between dysphagia and manometry result	Other Association with dysmotility	Conclusion
Putnam et al 1984	Prospective cohort study	33 consecutive EA patients of whom 20 agreed to be part of study	15M 5F 4months-12 years Dilatation in 20% Height and weight within normal limits	4mths-12yrs	Dysphagia 25% GER 0% Nocturnal cough 0%	Done in 19 Stricture 0% Slight anastomotic narrowing in 26% No GER seen in 79% 37% had ineffective peristalsis 57% of those with ineffective peristalsis had simultaneous contractions on manometry (the rest did not cooperate on manometry) Patients also had normal peristalsis in contrast study Half of patients with abnormal peristalsis on manometry had normal peristalsis in barium study.	Tuttle test: Micro pH probe placed 2cms above LES and 300mls of 0.1N HCl/1,73m2 instilled into stomach and acid reflux measured for over 60minutes Done in 17pts 86% were abnormal with pH<4 >15sec 67% of patients with abnormal tuttle test showed no reflux in barium study		Stationary Water perfused Sedation used in younger patients	UES resting pressure normal in 88% (>20mmHg) LES resting pressure normal in 90% (22+/-7mmHg) Distance between UES and LES increased with age (9-24cms) NS difference when compared to lengths in non EA children Motility assessed in 13pts 46% had peristaltic waves 54% had simultaneous contractions LES relaxation determined in 11 patients Normal (<9s) in 91% Amplitude of peristaltic waves normal in 85% (20-50mmHg) No correlation between amplitude and type of contraction	Of the 7 patients with simultaneous contractions in manometry 1 had dysphagia None of patients with slight anastomotic narrowing in barium study had dysphagia		Normal haematocrit and stool occult blood Barium study is not a sensitive way to determine GER Tuttle test is also not as sensitive as a 24 hour pH study to determine GER Correlation between various tests for esophageal function was not good. Concluded some tests might be too sensitive and have little clinical relevance

STUDY Author/ Year	DESIGN	Number Of subjects	Patient Characteristics	Follow up	Incidence Of Dysphagia	Contrast Study results	pH Metry results	Endoscopy results	Type of Manometry	Results of manometry	Association between dysphagia and manometry result	Other Association with dysmotility	Conclusion
Karanika et al 2011	Case control **Conference Abstract**	9 EA 8 controls	EA Age 8.2 (2-13) Type C Controls Age matched NERDS 7.5 (2-15)						EHRM Wet swallows Multiple rapid swallows Solid swallows	The mean number of peristaltic contractions was lower in EA as compared to controls (0.4+0.8 vs 8.3+0.5, P<0.001) The number of simultaneous contractions were significantly higher compared to controls (9.6+1 vs 0.1+0.4, P<0.001). No differences in the UESP (67.3+23 vs 63 +22, NS) No differences in LESP (14.1+7.6 vs 16.1+3.6, NS) were found between the 2 groups The proportion of patients with peristaltic pattern was significantly higher in controls vs EA (8/8, 100% vs 0/9,0%, P<0.001 Aperistaltic pattern characterized by simultaneous contraction was found in all children with EA (9/9, 100% vs 0/8 0%,			Profound esophageal motor abnormalities are ubiquitous in children with EA with an absence of normal peristaltic activity throughout the esophageal length despite a good anatomical result from surgery.

										P<0.001). In 2 EA patients (2/9, 22%) distal esophageal peristaltic activity was occasionally found. Peristaltic contractions were never recorded in the upper third of the esophagus in EA patients.			

<table>
<tr><th>Study
Author/Year</th><th>Type of study</th><th>Patient characteristics</th><th>Follow up</th><th>Dilatations</th><th>GER</th><th>Hospital stay</th><th>Dysphagia
And other symptoms</th><th>Conclusion
Other remarks</th></tr>
<tr>
<td>Koivusalo et al
2004</td>
<td>Retrospective review

Center A
Symptomatic dilatation
1986-1999

Center B
Routine dilatation
From 3wks then every 1-3wks until esophageal diameter of 10mm
1989-1999</td>
<td>Center A
63pts
35M, 28F

Center B
37pts
31M, 6F

No significant difference between:
birth weight
anastomotic leakage
Recurrent fistula
Severe tracheomalacia requiring aortopexy
Between 2 centers

Higher rate of associated anomalies 68% in centre B compared to centre A 35% (p=<.05)

Higher rate of major cardiac disease in centre B 38% compared to center a 17% (p=<.05)

Centre B used transpleural and center A used extrapleural approach

Center B routinely used chest drain for 4 days post op

Centre B routinely started NG feeds on day 4 and oral on day 8, where centre A started NG feeds when gastric volumes <10ml/4hours and oral if no siallorrhea</td>
<td>2 years</td>
<td>
<table>
<tr><th></th><th>A</th><th>B</th><th>P</th></tr>
<tr><td>Patient No</td><td>63</td><td>37</td><td></td></tr>
<tr><td>Number who had dilatation (%)</td><td>26 (41%)</td><td>37 (100%)</td><td><.05</td></tr>
<tr><td>Number of dilatations</td><td>107</td><td>256</td><td></td></tr>
<tr><td>Number/pt Median (range)</td><td>4 (2-11)</td><td>7 (3-20)</td><td><.05</td></tr>
<tr><td>Dilatation Complications</td><td>7/26</td><td>3/37</td><td>NS</td></tr>
<tr><td>First dilatation Age in wk Median(range)</td><td>5 (2-26)</td><td>3 (3-5)</td><td><.05</td></tr>
<tr><td>Last dilatation Age in week Median(range)</td><td>20 (2-96)</td><td>17.5 (6-58)</td><td>NS</td></tr>
</table>
Incidence of dilatation related complications was higher in center A 28% than in center B 11% (p=NS)
</td>
<td>Classified as follows:
GER

No GER
No symptoms and Normal contrast or Normal endoscopy or Normal 18hr pH study

Mild GER
Symptoms
+ve contrast
or pH<4 for 5-10%
or mild esophagitis

Severe GER
Severe symptoms
pH <4 for >10%
or severe esophagitis
or symptoms and investigations warranting ARS <1yr age

Center A 48% GER
Center B 51%
P=NS
No significant difference in severity of GER between centers

Center A pts with GER were more likely to need dilatations but the number of dilatations did not differ between patients with GER and those without GER

Anti reflux medication use
Center A 65%
Center B 54%
P=NS

23/26 dilated pts in center A had anti GER meds which was continued for 2mths post dilatation

Fundoplication
Center A 29%
Center B 32%
P= NS</td>
<td>Number of secondary hospitalisations for dilatation in Center A
Median (range)
4 (0-9)

Number of secondary hospitalisations for dilatation in Center B
Median (range)
5(0-9)
P=NS

Hospital stay for dilatation, days, mean (range)

Center A 6 (1-42)
Center B 13 (2-35)
P<.05

Primary hospital stay
Center A 24 (9-251)
Center B (33 (15-118)
P<.05

Secondary hospital stay not related to dilatation
Center A 6 (0-116)
Center B 11 (0-281)
P<.05</td>
<td>
<table>
<tr><th></th><th>A</th><th>B</th><th>P</th></tr>
<tr><td>Dysphagia</td><td></td><td></td><td>NS</td></tr>
<tr><td>None</td><td>49</td><td>29</td><td></td></tr>
<tr><td>Mild</td><td>17</td><td>8</td><td></td></tr>
<tr><td>Moderate</td><td>1</td><td>0</td><td></td></tr>
<tr><td>Severe</td><td>5</td><td>0</td><td></td></tr>
<tr><td>Respiratory</td><td></td><td></td><td>NS</td></tr>
<tr><td>None</td><td>25</td><td>24</td><td></td></tr>
<tr><td>Mild</td><td>24</td><td>11</td><td></td></tr>
<tr><td>Moderate</td><td>14</td><td>3</td><td></td></tr>
<tr><td>Severe</td><td>0</td><td>0</td><td></td></tr>
<tr><td>Bolus Obstruction</td><td></td><td></td><td>NS</td></tr>
<tr><td>No</td><td>50</td><td>30</td><td></td></tr>
<tr><td>Once</td><td>8</td><td>5</td><td></td></tr>
<tr><td>>Once</td><td>5</td><td>2</td><td></td></tr>
</table>
At 2years the overall frequency of dysphagia in center A was 36% and 21% in center B (P=NS)

5 pts in center A had severe dysphagia (3 due to severe GER, no stricture), 1 due GER stricture and 1 due to cyanotic heart disease
</td>
<td>Policy of dilatation on demand results in fewer procedures, fewer hospital stays, likely lower cost than the policy of routine dilatations of all patients with comparable medium term results

? longer primary and secondary hospitalisations due to higher incidence of associated anomalies

Risk of severe complication due to dilatations favours judicious use of dilatations</td>
</tr>
</table>

<table>
<tr><th>Study Author/Year</th><th>Type of study</th><th>Number of subjects</th><th>Patient characteristics</th><th>Follow up</th><th>Dilatations</th><th>GER</th><th>Dysphagia</th><th>Nutrition</th><th>Conclusion Additional remarks</th></tr>
<tr>
<td>Koivusalo et al 2009</td>
<td>Retrospective Chart review</td>
<td>Routine dilatation (RD) 46

Selective dilatation (SD) 35</td>
<td>RD between 1989-2002
34M, 12F
All type C

SD between 2002-2007
20M, 15F
All type C

No significant difference between both groups with respect to:

birth weight
Gestational age
Spitz classification
Anastomotic leakage
Long gap
Recurrent fistula
Severe tracheomalacia requiring aortopexy

RD gp had significantly more associated anomalies

All patients in Rd had transpleural approach to repair, but in SD 3 pts had extra pleural and 3 had thoracoscopic repair

All were on soft feeds till 2yrs age</td>
<td>3 years</td>
<td>In RD endoscopic dilatations started at 3wk post op and repeated every 1-3wks until stable anastomotic diameter of 10mm reached and endoscopically verified

In SD dilatations done in symptomatic pts with:
Dysphagia
Siallorrhea
Respiratory symptoms related to dilated upper pouch pressing on malatic trachea
Done endoscopically if anastomotic stricture seen

Hydrostatic Balloon dilatations in all but 1 where bougie used. Started at 6-8mm and proceeded to 10-12mm if possible

Prophylactic AB given

Number (%) of patients undergoing dilatations
<table><tr><th>Months after repair</th><th>RD</th><th>SD</th><th>p</th></tr><tr><td>0-6</td><td>46(100)</td><td>19(54)</td><td><.05</td></tr><tr><td>6-12</td><td>4(9)</td><td>12(34)</td><td><.05</td></tr><tr><td>12-24</td><td>2(4)</td><td>4/29(14)</td><td>NS</td></tr><tr><td>24-36</td><td>0(0)</td><td>2/19(11)</td><td>NS</td></tr><tr><td>total</td><td>46(100)</td><td>24(68)</td><td><.05</td></tr></table>
Cumulative number(%) of patients who had dilatations
<table><tr><th>Months after repair</th><th>RD</th><th>SD</th><th>p</th></tr><tr><td>0-6</td><td>46(100)</td><td>19/35(54)</td><td><.05</td></tr><tr><td>6-12</td><td>46(100)</td><td>22/35(68)</td><td><.05</td></tr><tr><td>12-24</td><td>46(100)</td><td>23/32(72)</td><td><.05</td></tr><tr><td>24-36</td><td>46(100)</td><td>17/25(68)</td><td><.05</td></tr></table>
In first 6mths significantly more dilatations in RD gp. 46% in SD had no dilatations in first 6mths.
From 6mths-3yrs fewer patients dilated in RD gp.
During 3yr F/U, 32% in SD gp had no dilatation at all.
In total RD gp had 321 and SD had 81</td>
<td>GER symptoms treated with sucralfate/ranitidine/omeprazole/cisapride

ARS done for refractory symptoms or if refractory stricture due to GER

At 1yr all patients had endoscopy and biopsy. Graded as per Hetzel
Grade 0-normal
Grade1-mild
Grade2-moderate
Grade3-Severe esophagitis

GER
0-12mths GER
RD 33%
SD 23% (P=NS)

>12mths after repair GER
RD 46%
SD 22%
P=NS

Median number of dilatations required in pts with GER:
RD 7(3-12)
SD 2(0-13), did not differ from those without GER:
RD 7(2-13)
SD 1(0-13)

Biopsy:
<1yr
RD 2 grade 0, 5 grade 1 (RD1, SD4)

At 1yr
RD
52% normal
36% mild
10% moderate
2% severe

SD
69% normal
28% mild
3% moderate
0% severe

The incidence of patients with moderate or severe esophagitis did not differ significantly between Rd (6/46) and SD (1/35), p=NS. There was no EE seen.

Grade of esophagitis at age 1 did not</td>
<td>At 12months
RD 17%
SD33%

At 24months
RD 13%
SD22%

At 36months
RD 11%
SD 16%
P=NS
At 24 and 36 months only mild dysphagia

At 12mths in 3pts in SD with dysphagia but no stricture it was related to heart disease and oral aversion

Food bolus obstruction

12months
RD 4%
SD 6%

24months
RD 9%
SD 6%

36months
RD 11%
SD 16%

Overall at 36months
RD 2%
SD 4%
P=NS</td>
<td>Change in relative weight
<table><tr><th>Months after repair</th><th>RD%</th><th>SD%</th><th>P</th></tr><tr><td>0-6</td><td>6 (-21-25)</td><td>5 (-8-35)</td><td>NS</td></tr><tr><td>6-12</td><td>-3 (-17-12)</td><td>-1.5 (-21-5)</td><td>NS</td></tr><tr><td>12-24</td><td>0 (-17-18)</td><td>0 (-7-11)</td><td>NS</td></tr><tr><td>24-36</td><td>0(-10-9)</td><td>0 (-7-6)</td><td>NS</td></tr></table>
Changes in relative weights did not differ between RD and SD groups</td>
<td>After repair of EA with distal fistula Selective dilatation (SD) resulted in significantly less dilatations than routine dilatations (RD) with equal long term results.

More liberal use of omeprazole in SD group between 2002-2007 which may have decreased need for ARS</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>dilatations overall.
Overall 70% in SD had dilatation and 100% in RD.

Median number of dilatations/patient

<table>
<tr><th>Months after repair</th><th>RD</th><th>SD</th><th>P</th></tr>
<tr><td>0-6</td><td>7(1-13)</td><td>3(1-13)</td><td><.05</td></tr>
<tr><td>6-12</td><td>3(1-12)</td><td>1(1-6)</td><td><.05</td></tr>
<tr><td>12-24</td><td>1(1-2)</td><td>1</td><td>NS</td></tr>
<tr><td>24-36</td><td>0</td><td>1</td><td>NS</td></tr>
<tr><td>Total</td><td>7(2-23)</td><td>3(1-16)</td><td><.05</td></tr>
</table>

Incidence of complication was0.6% in Rd and 1% in SD, p=NS
Severe dilatation associated complications:
RD 2(4)
SD 1 (3)
P=NS

1 pt in RD with recalcitrant stricture required resection</td>
<td>correlate with number of dilatations (r=0.191, p=NS)

Fundoplication or anti reflux surgery (ARS)

First year after repair
RD 11
SD 3
P=NS
>1yr after repair
RD5
SD1
P=NS

The number of dilatations in patients who had ARS 7(5-12) in RD and 3 (1-4) in SD did not differ from those who did not have ARS, RD 7(2-13) and SD 1(0-13), p=NS</td>
<td></td>
<td></td>
<td></td>
</tr>
</table>

Study Author/Year	Type of study	Number of patients	Patient characteristics	Methods	Results	Conclusion Other remarks
Qi et al 1997	Animal Model Case cohort	14/21 Adriamycin treated rat fetuses developed EA-TEF 6 control rat fetuses were injected with saline during corresponding period in gestation	Fetuses harvested by cesarian section in day 21 of gestation	Slides from all animals observed in cephalocaudal direction from level of cricoid down to diaphragmatic crura to map out course of vagus nerve (VN) and recurrent laryngeal nerve (RLN) and their branches	Fewer branches from both RLN in EA-TEF rat fetuses Deviation of the left VN from its normal course below the aorta, passing behind the fistula to approach and join with the right vagus to form a single nerve trunk on the right side of the esophagus Relatively few branches from the single VN trunk (composed of fibres from right and left vagus) on the surface of the lower esophagus resulting absence of peri esophageal plexus which normally penetrates esophageal wall to innervate the esophagus	Normal esophageal function depends on integral intrinsic intramural nervous system and intact extrinsic system. This study shows congenital abnormalities in course and branching pattern of VNs as they descend in the thorax. There was also relative deficiency in the nerve fibre plexus in the rat fetuses affected with EA-TEF The left VN changed from it's normal course to reach the right side without forming the peri esophageal plexus, the left wall of the distal esophagus may have an even sparser innervation compared to the right ? the presence of a fistula arising from the right main bronchus may prevent the left VN from moving from the left to the anterior surface of the esophagus as it descends ? In addition surgical mobilization and dissection could further damage the vagi thereby worsening the degree of esophageal dysfunction, resulting in dysphagia and GER Need to be cautious about extrapolating findings from animal study to humans

<table>
<tr><th>Study
Author/Year</th><th>Type of study</th><th>Number of patients</th><th>Patient characteristics</th><th>Methods</th><th>Results</th><th>Conclusion
Other remarks</th></tr>
<tr>
<td>Qi et al
1999</td>
<td>Animal model of EA-TEF study

Case control study</td>
<td>48 control rat fetuses

40 EA-TEF rat fetuses after injection of Adriamycin

6 rat fetuses without EA-TEF after injection of Adriamycin</td>
<td>Number of esophageal specimens stained with each antibody
<table>
<tr><th>Group</th><th>NSE</th><th>VIP</th><th>SP</th><th>CGRP</th></tr>
<tr><td>Control Stretched</td><td>4</td><td>5</td><td>5</td><td>4</td></tr>
<tr><td>Control stripped</td><td>9</td><td>6</td><td>9</td><td>6</td></tr>
<tr><td>Treated intact</td><td>2</td><td>2</td><td>1</td><td>1</td></tr>
<tr><td>EA-TEF</td><td>12</td><td>8</td><td>10</td><td>10</td></tr>
</table>
</td>
<td>Whole mount preperations of each esophagus were stained with fluorescent antibodies against:
Neuron specific enolase (NSE)

Vaso active intestinal peptide (VIP)

Substance P (SP)

Calcitonin gene related peptide (CGRP)</td>
<td>Compared with control rat fetuses the density of the nerve plexus, ganglia and number of cell bodies per ganglion immunostained by NSE, VIP or SP were significantly reduced in the esophageal body in EA-TEF fetuses

Density of ganglia stained with NSE were reduced in GE junction in controls but in EA-TEF the ganglia were slightly increased in GEJ, but normal configuration was not seen

VIP immunoreactivity at GEJ was higher than esophageal body in EA-TEF unlike that seen in controls and it was also higher in GEJ in EA-TEF compared to controls

In the esophageal body and GEJ there were no SP immunoreactive cell body seen in EA-TEF compared to controls

CGRP immunoreactive nerve fibers in the esophageal wall of both controls and EA-TEF fetuses were connected with extrinsic nerve bundles. However the density of the CGRP immunoreactive nerve fibers and branching frequency was decreased in EA-TEF compared to controls</td>
<td>Significant abnormalities of the intramural nervous components of the esophagus of the EA-TEF rat fetuses involving the ganglia (NSE labeled) and both the excitatory (SP labeled) and inhibitory (VIP labeled) intramural nerves were seen

The continuity of nerve fibers between the trachea and the esophagus and the increased number of ganglia at the GEJ (where there are very few normally) may represent abnormal esophageal innervation in EA-TEF resulting from the presence of EA-TEF in early embyogenesis

Compared with controls the number of cell bodies within ganglia and density of ganglia and nerve fibres in the myenteric plexus was significantly reduced in EA-TEF. This may result in esophageal dysmotility resulting in dysphagia and GER</td>
</tr>
</table>

STUDY **Author/ Year**	**DESIGN**	**Number** **Of subjects**	**Patient** **Characteristics**	**Study Method**	**ICC** **Immuno-histochemistry (mean frequency of ICC evaluated by visual score)**	**ICC** **Mean frequency evaluated by Morphocytometry**	**ICC** **Transmission Electron Microscopy**	**Conclusion** **Additional remarkrs**
Midrio et al 2010	Case control study	15 neonates with EA and distal TEF 10 control neonates who dies from non-esophageal diseases	**EA** Full term Mean birth weight 3390g (2900-3725) Mean age of surgery 20hours Mean gap 1.7cms (1.5-2) Sample from tip of upper pouch and tip of TEF **Controls** Mean time of death 60hours (1-480) Sample from level of carina in proximal esophagus and 4cms distally for distal esophagus	Samples processed for : ICC identification with c-kit immunohistochemistry Semi quantitative analysis done with a visual score for ICC-IM (intramuscular ICC) and ICC-MY (Myenteric ICC) Grade 0-Absent Grade 1-Very low Grade 2-Low Grade 3-Medium Grade 4 –High Grade 5-Very high ICC morphocytomeyry Transmission electron microscopy	**<u>ICC (IM)</u>** EA upper pouch Grade 3 - 87% Grade 4 - 13% Mean (SD)3.1(0.4) EA-TEF Fistula Grade 0 – 7% Grade 1- 20% Grade 2- 40% Grade 3- 33% Mean(SD) 2 (0.9) Controls Proximal esophagus Grade 3- 20% Grade 4- 50% Grade 5- 30% Mean (SD) 4.1(0.7) Controls Distal esophagus Grade 3- 60% Grade 4- 40% Mean (SD) 3.4(0.5) In controls significantly more ICC (IM) in proximal esophagus compared to distal (p=0.013) In EA-TEF, Significantly more ICC (IM) in upper pouch compared to fistula (p=0.0001) **<u>ICC (MY)</u>** EA upper pouch Grade 0 - 53% Grade 1- 47% Mean (SD) 0.46(0.51) EA-TEF Fistula Grade 0 – 73% Grade 1- 27% Mean(SD) 0.26 (0.45)	Results expressed as a % of the area occupied by c-kit positivity Upper Pouch 17.92 (SD 9.89) Proximal esophagus 30.65(12.92) Significantly higher frequency of ICC in proximal esophagus compared to upper pouch, p=0.001 Fistula 7.97(7.33) Distal esophagus 18.04(7.68) Significantly higher frequency of ICC in distal esophagus compared to fistula, p=0.003	Tissue from both EA-TEF and controls showed signs of hypoxia ICC from upper pouch in EA-TEF was immature with fibroblast like features. Immature ICC are c-kit negative. Differentiation of ICC is delayed in EA which results in scarcity of c-kit +ve cells ICC from controls showed typical features with characteristic relations to smooth muscle cells and nerve endings	First study to look at ICC in EA-TEF Cranio-caudal distribution of ICC in both cases and controls. As there is an aboral progression of neural crest derived cells, in EA this especially affects distal esophagus and? LES. Showed ICC significantly reduced in EA compared to controls. Especially true for those in myenteric plexus which are ICC mainly involved in peristalsis. The reduction in ICC-MY is associated with an equivalent reduction myenteric plexus ganglia. ICC in EA are also more immature. And formation of ICC networks is affected. ?This is responsible for impaired peristalsis, dysphagia and GER

					Controls Proximal esophagus Grade 1- 40% Grade 2- 50% Grade 3 - 10% Mean (SD) 1.7(0.67) Controls Distal esophagus Grade 1- 60% Grade 2 - 30% Grade 3 – 10% Mean (SD) 1.5 (0.7) In control, More ICC (MY) in proximal esophagus compared to distal but p=NS (p=0.89) In EA-TEF, No significant differences between upper pouch and fistula samples in ICC (MY) P=0.658 Significantly higher mean frequency of ICC in proximal esophagus compared to upper pouch (p=0.0002) Significantly higher mean frequency of ICC in distal esophagus compared to fistula (p=0.0015) Overall c-kit positivity was significantly reduced in EA-TEF compared to controls			

STUDY Author/ Year	DESIGN	Number Of subjects	Patient Characteristics	Follow up	Incidence Of Dysphagia	Contrast Study results	pH Metry results	Endoscopy results	Type of Manometry	Results of manometry	Association between dysphagia and manometry result	Other Association with dysmotility	Conclusion Additional Remarks
Dutta et al 2001	Prospective case control	27 cases 25 age matched controls	**EA** mean age 6-108 months Mean 30.5+/-30.3months 14M 13F All EA were EA with distal TEF 1 had anastomotic leak 1 had stricture requiring dilatation **Controls** mean age 36.8+/-22.6months 20M 5F Controls admitted for surgery in areas other than esophagus and GIT		Desjardin criteria used for evaluation: Excellent (asymptomatic) 41% (11pt) Good (occasional dysphagia) 37% (10pts) Fair (Frequent dysphagia) 59% (6pts)	Radionuclide study used to evaluate GER depending on extent of reflux in esophagus Mild 22% (6) Moderate 7.5% (2) Severe 11% (3)			Stationary Water perfused	All controls had normal manometry **EA patients** **1.UES** pressure and relaxation with swallowing normal in 96% **2.Peristalsis** : a. Progressive peristaltic waves of good amplitude 8% b. Occasional peristaltic waves 33% c. Low amplitude simultaneous non-propulsive contractions 59% **3. Mean pressure in esophageal body** 12.4+/-5.5mmHg in EA and 21.1 +/-6.9mmHg in controls p <0.002 **4. Mean peak pressure in esophageal body** 34.9+/-20.4 in EA and 62.3 +/-19.3mmHg in controls, p <0.004	**1. Mean esophageal body pressure** No dysphagia (excellent group) 48.2+/-19.4mmHg Occasional dysphagia (Good) 33.8+/-19.2mmHg Frequent dysphagia (Fair) 29.4+/-18.3mmHg P=NS **2. Mean LES pressure** No dysphagia 12.5+/-7.2mmHg Occasional dysphagia 11.8+/-7.5mmHg Frequent dysphagia 9.3+/-4.9mmHg P=NS **3. Peristalsis** No dysphagia gp 45% occasional peristalsis 9% good peristalsis No peristalsis 46% Occasional dysphagia gp Occasional peristalsis 30%	**1. GER** No dysphagia gp No GER 45% Mild GER 55% Occasional dysphagia gp No GER 60% Moderate GER 20% Severe GER 20% Frequent Dysphagia gp No GER 83% Severe GER 17% **2. GER and LES** No GER, LES was 12+/-7.1mmHg Mild GER LES was 12.3+/-3.7mmHg Moderate GER, LES was 11+/-5.7mmHg Severe GER, LES was 6.9+/-5.6mmHg P=NS	Radionuclide study used to grade GER not pH metry Pressure and contractily profile was abnormal in majority of patients Poor correlation between symptoms and manometry results, as manometry was abnormal even in absence of symptoms.

										4. Mean LES pressure 12.2+/-6.8mmHg in EA and 16.8+/-4.3 in controls, p<0.0001	Good peristalsis 10% No peristalsis 60% Frequent dysphagia gp Occasional peristalsis 17% No peristalsis 83%		

Dysphagia and esophageal function in EA-TEF

STUDY Author/ Year	DESIGN	Number Of subjects	Patient Characteristics	Follow up	Incidence Of Dysphagia	Contrast Study results	pH Metry results	Endoscopy results	Type of Manometry	Results of manometry	Association between dysphagia and manometry result	Other Association with dysmotility	Conclusion Additional Remarks
Shono et al 1993	Case series	2	1F 32 wks Gestation Initial gap distance 4 vertabrae Gap distance post stretching with Nelaton rubber catheter was 1 vertebra at 7months Primary anastomosis at 9 months Stretching done from 3-7 months 1M, 36 wks gestation Initial gap -8 vertebra Stretching initiated at 17 days. Gap distance at 5 months -4 vertebra Pre operative manometry done at 6 months Anastomosis done using gastric tube at 15 months Both patients had gastrostomy	9-15months					Stationary Water perfused Sedation	Pre operative manometry done at 7 months in patient 1 and 6 months in patient 2 **Resting pressure in upper esophagus** was negative in both patients (-6 and -3cms H2O) preoperatively **Resting pressure in lower esophagus** was negative in patient 1 (-6cms H2O) and 0 in patient 2 **LES** 48cmsH2O in patient 1 and 0 in patient 2 (distal esophagus too short to form LES mechanism in pt 2) **Peristalsis** Peristalsis in proximal esophagus with swallowing was followed by coordinated contraction in distal esophagus and reflex relaxation of LES in both patients Post operative manometry done at 1 and 3 months post primary anastomosis in patient 1			Preoperatively normal coordinated peristalsis with swallowing was seen in proximal and distal esophagus Mechanism of LES is present in distal esophagus which relaxes normally with swallows Preoperative elongation procedures produces no effects on motility in proximal and distal esophagus Abnormal motility post operatively suggests role of intra operative dissection and mobilisation and denervation Although Romeo's study showed abnormal motility preoperatively that study was done in new born period when esophageal motility may not be fully developed even in normal infants

										Post operatively resting pressure in upper esophagus was negative in patient 1 **Resting pressure in lower esophagus** was negative post operatively in patient 1 (-8cms H2O) **LES** pressure post operatively was 28 at 1month and 36cmsH2O at 3 months **Peristalsis** Simultaneous contractions with swallowing in proximal and distal esophagus and incomplete relaxation of LES			

Dysphagia and esophageal function in EA-TEF

STUDY Author/ Year	DESIGN	Number Of subjects	Patient Characteristics	Follow up	Incidence Of Dysphagia	Contrast Study results	pH Metry results	Endoscopy results	Type of Manometry	Results of manometry	Association between dysphagia and manometry result	Other Association with dysmotility	Conclusion Additional Remarks
Takano et al 1988	Case control	15 with Type C EA 30 controls 8 Hiatal hernia 6 esophageal varices	Controls <1yr 10 1-5yrs 10 5-10yrs 10		GER symptoms 40% No GER symptoms 60%	GER seen in 40% No GER seen in 60%			Minimum anaesthesia in infants No anaesthesia in older kids Stationary Water perfused Wet and dry (air) swallows 2-5mls in infants 5-10ml in older kids GER inducing test: Upper abdomen pressed and if lower esophageal pressure increased with relaxation of LES test was considered +ve	**Controls** LES Average pressure 23.8+/-8.4cmH2O Length 2.1+/-0.8cm LES relaxation test (swallows) Complete relaxation 100% GER inducing test Negative 100% **EA patients** GER (-ve) LES pressure 23.4+/-6.5cmH2O Length 12.1+/-0.6cms LES relaxation Complete 67% Slow 33% Absent 0% GER Inducing test: Negative 100% GER (+ve) LES pressure 16.3+/-3.7cmH2O Length 1.3+/-0.2cms LES relaxation Complete 0% Slow 40% Absent 60% LES pressure was significantly higher and LES			Livaditis procedure (muscle lengthening myotomy) does not affect LES function.

										was longer in GER+ve vs GER –ve 2 patients with EA and hiatal hernia had anti reflux surgery and LES pressure and length improved post fundoplication. But contractions were still simultaneous LES relaxation was still present GER Inducing test: Positive 100% Peristalsis in lower esophagus: Peristaltic contractions 0% Simultaneous contractions 100% regardless of presence of GER 2 patients who had myotomy (Livaditis procedure) at time of repair had normal LES pressure, length and relaxation with swallow and were –ve on GER inducing test			

Dysphagia and esophageal function in EA-TEF

STUDY Author/ Year	DESIGN	Number Of subjects	Patient Characteristics	Follow up	Incidence Of Dysphagia	Contrast Study results	pH Metry results	Endoscopy results	Type of Manometry	Results of manometry	Association between dysphagia and other symptoms and manometry result	Other Association with manometry results	Additional Remarks
Lemoine et al 2013	Retrospective Case series	40	25M 15F Median age 8yrs (11mths-18yrs) **35 (87%)Type C EA** 23anastomotic leak 1 early anastomotic stricture 10 fundoplications 11 strictures 10dilatations I2done <1yr from HREM **5 (13%)Type A EA** 2 anastomotic leak 1 early anastomotic stricture 3 fundoplications 3 strictures 3 dilatations I done <1yr from HREM **6(16%) long gap** (4Type A, 2 Type C) 14(35%) other anomalies		Dysphagia 45% Change in feeding habits 73% GER 38% Respiratory 38% Asymptomatic 18%		13 (33%) had pH monitoring GER in 39%	21(53%) had gastroscopy 24% esophagitis on biopsy 24% strictures	HREM Solid state catheter No sedation 36 channels 12 pressure sensing points 2 sizes (2.75/4.2mm) 10 Wet swallows 2mls if <5yrs 5mls if >5yrs 33pts 10 swallows 4 did <7 1<4 Normal reference values (25th-75th centile) as per Goldani et al	3 Types No patient exhibited normal peristaltic pattern **<u>APERISTALSIS</u>** 15(38%) UES Residual pressure (<12mmHg) 7.9mmHg (-5.2-11.8) LES Basal Pressure (15-31mmHg) 7.8mmHg (5.6-15.4) Hypertonic (>32mmHg) 1(7%) Hypotonic 7(47%) IRP (<15mmHg) 3.5mmHg (2.2-8.9) Normal IRP 14(93%) **<u>PRESSURIZATION</u>** 6 (15%) UES Residual pressure (<12mmHg) 6.2mmHg (0-16.6) LES Basal Pressure (15-31mmHg) 19.9mmHg (2.4-51.5) Hypertonic (>32mmHg) 1(17%) Hypotonic 2(33%) IRP (<15mmHg) 7.9mmHg (0.1-22.4) Normal IRP 5(83%) Esophageal Body	**Dysphagia (18)** Aperistalsis 4(22%) Pressurization 4(22%) Distal contraction 10(56%) -Change in feeding habits (29) Aperistalsis 9(31%) Pressurization 4(14%) Distal contraction 16(55%) **GER (15)** Aperistalsis 6(40%) Pressurization 4(27%) Distal contraction 5(33%) **Pulmonary symptoms (15)** Aperistalsis 7(47%) Pressurization 4(27%) Distal contraction 3(20%) -Asymptomatic (7) Aperistalsis 4(57%) Pressurization 1 (14%) Distal contraction 2 (29%)	**EA type** Type A (5) Aperistalsis 3 (60%) Pressurization 2 (40%) Distal contraction 0 Type C(35) Aperistalsis 12 (34%) Pressurization 4 (11%) Distal contraction 19 (54%) Long gap (6) Aperistalsis 4 (67%) Pressurization 2 (33%) Distal contraction 0 -**Post operative complications** **Anastomotic leak** (6) Aperistalsis 4 (67%) Pressurization 1(16%) Distal contraction 1 (16%) **Early anastomotic stricture (3)** Aperistalsis 1(33%) Pressurization 2(66%) Distal contraction 0	First study to use HREM to characterize motility patterns post EA repair in children 3 main types Complete Aperistalsis Pressurization Simultaneous contraction of entire esophageal body length following deglutition associated with EGJ relaxation) Distal contraction with evidence of middle third or distal third esophageal contraction. DCI and DCIa were low in this gp ? due to abnormal innervation/ smooth musculature of distal esophagus /or short distal peristaltic esophagus or both Long TZ ? responsible for dysphagia Although 4 pts with pressurization pattern had previous fundoplication , but LES pressure and relaxation in these pts was similar to other groups.

										DISTAL CONTRACTION 19(48%) UES Residual pressure (<12mmHg) 5.9mmHg (3.3-13.516.6) LES Basal Pressure (15-31mmHg) 30.5mmHg (18.6-36.3) Hypertonic (>32mmHg) 9(47%) Hypotonic 2(11%) IRP (<15mmHg) 12.2mmHg (4.3-14.5) Normal IRP 51158%) Esophageal Body DCI (2311-3149mmHg/cm/s) 302mmHg/cm/s (72-437) DCIa (161-259mmHg/s) 13.4mmHg/s (3.4-23.1) CFV (2.5-4.1cms/s) 1.6cms/s (-8-5.6) Transition Zone 7.6cm (6.3-9.6)		**Late anastomotic stricture (14)** Aperistalsis 4 (29%) Pressurization 4 (29%) Distal contraction 5 (38%) **Pneumatic dilatation required (13)** Aperistalsis 4 (31%) Pressurization 4(31%) Distal contraction 5 (38%) **Fundoplication (14)** Aperistalsis 8 (57%) Pressurization 4(29%) Distal contraction 2 (14%) **Esophagitis (7)** Aperistalsis 4(57%) Pressurization 3(43%) Distal contraction 0 **Stricture on endoscopy (5)** Aperistalsis 2(340%) Pressurization 2(40%) Distal contraction 1 (20%)	But pre and post-operative studies were not done. Long gap/anastomotic leaks/severe esophagitis seen more in aperistaltic group **Esophageal motility patterns were not predictive of symptoms** Asymptomatic pts were seen in all 3 groups Although esophagitis was seen in aperistalsis and pressurization groups not all patients had esophagoscopy Limitation: Retrospective nature so some data collected were incomplete

Study **Author/year**	**Type of Study**	**Number of patients**	**Patient characteristics**	**Method**	**Results** **Morphologic and immunohistochemical findings in EA-TEF**	**Conclusion** **Additional remarks**
Li et al 2007	Case control	24 EA-TEF 10 control specimens from neonates who died of non-esophageal diseases	24 Type 3 EA-TEF Biopsies taken from distal esophageal fistula Controls Specimens taken from mid esophagus	2 pathologists and 2 histologists examined all specimens 1 from each group was blinded to clinical information Specimens subjected to" Routine pathologic study Ultrastructural observation Immunohistochemical staining for: Neuron specific enolase (NSE) Substance P Vasoactive intestinal peptide (VIP) Nitric oxide synthase (NOS)	**Pathologic features** Meissners plexus well developed in both groups. In EA-TEF there was dysplasia of the Auerbach's plexus with reduced ganglia and thickened nerves and immature nerve cells. Ganglia number per plexus was significantlt reduced in EA-TEF compared to controls (P<.05) **Ultrastructural findings** EA-TEF Different to the controls in EA-TEF the intramuscular connective tissue was loose and slender. Endoplastic reticulum of smooth muscle cells was dilated. Mitochondria were distributed along cell membrane (in controls mitochondria were alongside nuclei) The ratio of granulated vesicles (containing noradrenaline) to clear vesicles (containing acetylcholine) in the varicosity of the intramuscular nerve ending was significantly higher than in controls (P<.05) **Immunohistochemistry** Positive expression of NSE (20.8%) and substance P (12.5%) seen in EA-TEF were significantly lower than in controls, where NSE was 90% and substance P was 80%, p=.000 for both VIP (83.3%) and NOS (75%) positivity in EA-TEF was significantly higher than in controls VIP 30%) and NOS 10%), p=.002 and p=.001 respectively.	Imbalance of neurotransmitter excretion in nerve vesicle, abnormal intrinsic dysplasia of nerve plexus and decreased expression of NSE and substance P and increased expression of VIP and NOS was seen in EA-TEF. This may result in worsened energy supply to smooth muscle cells and imbalance adrenergic and cholinergic nerve tone resulting in abnormal contraction and relaxation in the esophagus in EA-TEF resulting in dysphagia, GER and feeding difficulty. However biopsies taken from distal fistula may not be representative of entire esophageal structure in EA-TEF

Other GI anomalies(apart from ano-rectal) associated with EA-TEF

<table>
<tr><th>Author/Year</th><th>Study type</th><th>Number of patients with
Duodenal Atresia(DA)
Duodenal Stenosis (DS)

Patient characteristics</th><th>Results
Survival</th><th>Conclusion</th></tr>
<tr>
<td>Ein et al
2006</td>
<td>Retrospective review of 30yrs
1971-2000</td>
<td>24 with DA or DS

<table>
<tr><th></th><th>DA</th><th>DS</th><th>Total</th></tr>
<tr><td>EA</td><td>6</td><td>1</td><td>7</td></tr>
<tr><td>EA-TEF</td><td>9</td><td>8</td><td>17</td></tr>
<tr><td>Total</td><td>15</td><td>9</td><td>24</td></tr>
</table>

17M, 7F
Av birth weight 2100gms (1130-3450)
Av gestational age 35wks (30-39)
Associated anomalies 18(75%)
Gastrostomy done in 19 with repair
Follow up -3years

6% of all EA-TEF /EA had DS or DA during study period</td>
<td>18 survived (75%)

<table>
<tr><th></th><th>DA</th><th>DS</th><th>Survival %</th></tr>
<tr><td>EA</td><td>3/6 (50%)</td><td>0/1 0</td><td>3/7 (43%)</td></tr>
<tr><td>EA-TEF</td><td>7/9 (77%)</td><td>8/8 (100%)</td><td>15/17 (88%)</td></tr>
<tr><td>Survival %</td><td>10/15 (66%)</td><td>8/9 (88%)</td><td>18/24 (75%)</td></tr>
</table>

Av BW of survivors 2100gms
Av BW of non survivors 2300gms

Av Gestational age of survivors 35 weeks
Av gestational age of non survivors 34 weeks

Esophageal atresia repaired first in 5, 2/5 died.
Diagnosis of DA/DS overlooked in 4/5

Duodenal lesion repaired first in 11, all survived

EA and DA/DS repaired at same time in 7, 4/7 survived

Mortality of EA>EA-TEF
Mortality of DA>DS

Presence of associated anomalies did not affect survival

Cause of death:
Respiratory distress 3/6
Sepsis from disruption of EA anastomosis 2/6
Intra ventricular hemorrhage (had gastrostomy before DA recognized) 1/6

However there was also increased incidence of respiratory distress among non survivors who were operated on pre 1990</td>
<td>Coexistence of DA/DS must be considered in EA as delay in diagnosis can adversely affect outcome.

Diagnosis of DA/DS can be made by plain xray or in pure EA ultrasound or instillation of contrast into gastrostomy might be needed

In 4 only after gastrostomy feeds failed was diagnosis made. 2/4 died.

Staged repair of patients with EA and DA/DS is preferable.

In this study 83% of those who had staged repair survived compared to 57% of those whose repairs were not staged.

Staging (days/weeks) with repair of Da/DS first allows :
Growth
Improvement in pulmonary function
Some resolution of delayed gastric emptying seen after repair of DA/DS.
Hence esophageal anastomosis is less stressed by DGE and GERD
Allows growth of esophageal segments</td>
</tr>
</table>

Other GI anomalies(apart from ano-rectal) associated with EA-TEF

<table>
<tr><th>Author/Year</th><th>Study type</th><th>Number of patients with Duodenal Atresia(DA)

Patient characteristics</th><th>Results
Operative approach
Survival</th><th>Conclusion</th></tr>
<tr>
<td>Spitz et al
1981</td>
<td>Retrospective review over 15 yrs
1964-1978</td>
<td>18 with EA/EA-TEF + DA

BW 2+/-.45(1.2-2.8)
11M, 7F
16Type C
2 Type A
All 18 were group C Waterston

50 additional anomalies seen:
Genitourinary 11
Cardiac 9
Anorectal 8
Vertebral 4
Downs 2</td>
<td>Early survival rate 33%

<table>
<tr><th>Operation</th><th>Alive</th><th>Dead</th><th>Total</th></tr>
<tr><td>Repair EA and DA at same time</td><td>2</td><td>2</td><td>4</td></tr>
<tr><td>EA repaired first</td><td>2</td><td>1</td><td>3</td></tr>
<tr><td>DA repaired first</td><td>1</td><td>4</td><td>5</td></tr>
<tr><td>No TEF DA repaired</td><td>1</td><td>1</td><td>2</td></tr>
<tr><td>No surgery</td><td>0</td><td>4</td><td>4</td></tr>
<tr><td>Total</td><td>6</td><td>12</td><td>18</td></tr>
</table>

Anomalies incompatible with survival 4
Death due to associated anomalies 5</td>
<td>Diagnosis of DA done with xray or in pure EA when bilious reflux seen on gastrostomy or by instilling contrast in gastrostomy

Post repair of DA there is period of prolonged ileus resulting in duodeno-gastric reflux and GERD.

Hence suggest repair of EA, large caliber gastrostomy, duodenoduodenostomy and placement of a transanastomotic feeding tube.

If no TEF, suggest do repair DA, gastrostomy with trans anastomotic feeding tube and repair EA later.

EA repaired first (except pure EA) in all 5 long term survivors.

2/5 long term survivors had subsequent fundoplication.</td>
</tr>
</table>

Other GI anomalies(apart from ano-rectal) associated with EA-TEF

Author/Year	Study type	Number of patients with Malrotation Patient characteristics	Conclusion
Upadhyay et al 2000	Retrospective review of all EA cases between 1978-1997 Review of radiology done on these patients If malrotation not mentioned films reviewed by radiologist	91 patients with EA 60 (65.9%) had upper GI contrast series 3 (5%) had malrotation 1 had Ladd's procedure 1 not operated upon (Noonan's syndrome) 1 lost to follow up	There is risk for mid gut volvulus with malrotation Hence recommend routine post-operative study of upper GI tract be continued to establish rotation of small intestine. In patients with pure OA, at time of gastrostomy, malrotation of small intestine should be searched for.

Other GI anomalies(apart from ano-rectal) associated with EA-TEF

Author/Year	Study type	Number of patients with CDH-EA Patient characteristics	Results	Conclusion
Ben-Ishay ey al 2013	Retrospective review Congenital Diaphragmatic Hernia Study Group (CDHSG) was queried from Jan 2000-August 2011 The registry has 79 centers from 10 countries around the world Patients with CDH-EA were identified Primary end point was survival Secondary end point was to identify variables that explain variances in outcomes	4888 with CDH 23 (0.5%) had associated EA 19/23 (83.3%) had an associated TEF Mean gestational age of CDH/EA 33.8wks and 60.8% were preterm and 57.1% had surfactant	Nearly all CDH/EA had patch repair which suggests large defect Overall survival of CDH/EA was significantly lower 26.1% than registry mean 70.3%, p<.001 Survival of CDH/EA prems was 14.1% CDH/EA had less CDH repairs (52% vs 83%), p<.001 CDH/EA had more patch CDH repairs (95.7% vs 60.7%), p<.001 All 6 survivors had CDH repair, while only 6/17 non survivors had CDH repair CDH/EA had lower birth weight (1.8 vs2.94kg), p<.001 CDH/EA had more cardiac anomalies, p=.013 Associated anomalies were common in CDH/EA-82.6% (GIT 26.1%-imperforate anus, DA, DS, annular pancreas, anal stenosis) CDH/EA had more chromosomal anomalies, 21.7% vs 4.9%, p<.001 Logistic regression identified birth weight, cardiac anomalies, repair being done and surfactant administration to be significantly associated with adverse outcomes. EA was the only variable not independently associated with survival, although EA was present significantly more in the non survivor group	CDH/EA cohort has lower birth weight, more cardiac and chromosomal anamolies, higher surfactant use, larger defects needing patch repair compared to CDH without EA. Study limitations include retrospective nature and CDH orientation of cohort with no details on procedures other than CDH repair.

Other GI anomalies(apart from ano-rectal) associated with EA-TEF

<table>
<tr><th>Author/Year</th><th>Study type</th><th>Number of patients with EA-HPS (hypertrophic Pyloric Stenosis)

Patient characteristics</th><th>Results</th><th>Conclusion</th></tr>
<tr>
<td>Van Beelan et al
2014</td>
<td>Retrospective review

All cases of EA between 1988-2012 at single center

Incidence of EA-HPS in this cohort

Investigate known risk factors for EA-HPS
Primigravida
Caesarean section
Twin
Born in summer/spring
Type of feeding
Use of erythromycin</td>
<td>267 EA

20 EA-HPS (7.5%)</td>
<td>
<table>
<tr><th></th><th>EA-HPS</th><th>EA</th><th>P</th></tr>
<tr><td>Males</td><td>18(90%)</td><td>150 (6%)</td><td>.031</td></tr>
<tr><td>Gestational age</td><td>38 (2%)</td><td>37 (3%)</td><td>NS</td></tr>
<tr><td>Prematurity</td><td>6 (30%)</td><td>84 (34%)</td><td>NS</td></tr>
<tr><td>BW mean (SD)</td><td>2.9 (0.7)</td><td>2.6 (0.7)</td><td>.02</td></tr>
<tr><td>SGA</td><td>4 (20%)</td><td>38 (15%)</td><td>NS</td></tr>
<tr><td>Died</td><td>1 (5%)</td><td>10 (4%)</td><td>NS</td></tr>
<tr><td>Type of EA</td><td></td><td></td><td>NS</td></tr>
<tr><td>A</td><td>NA</td><td>21 (8%)</td><td></td></tr>
<tr><td>B</td><td>NA</td><td>NA</td><td></td></tr>
<tr><td>C</td><td>18 (90%)</td><td>220 (89%)</td><td></td></tr>
<tr><td>D</td><td>1 (5%)</td><td>1 (1%)</td><td></td></tr>
<tr><td>E</td><td>1 (5%)</td><td>5 (2%)</td><td></td></tr>
<tr><td>EA Surgery</td><td></td><td></td><td>NS</td></tr>
<tr><td>Thoracotomy</td><td>17 (85%)</td><td>193 (78%)</td><td></td></tr>
<tr><td>Thoracoscopy</td><td>2 (10%)</td><td>48 (19%)</td><td></td></tr>
<tr><td>Converted</td><td>1 (5%)</td><td>4 (2%)</td><td></td></tr>
<tr><td>No surgery</td><td>NA</td><td>2 (1%)</td><td></td></tr>
</table>
Risk factors for HPS
<table>
<tr><th>Risk Factors</th><th>EA-HPS n=20</th></tr>
<tr><td>Primigravida</td><td>5 (25%0</td></tr>
<tr><td>Twin</td><td>NA</td></tr>
<tr><td>Caesarean</td><td>1 (5%)</td></tr>
<tr><td>Relatives with HPS</td><td>2 (8%)</td></tr>
<tr><td>Season of birth</td><td>5 (25%)</td></tr>
<tr><td>Spring</td><td>2 (10%)</td></tr>
<tr><td>Summer</td><td>7 (35%)</td></tr>
<tr><td>Type of Feeding</td><td>2 (10%)</td></tr>
<tr><td>Breast milk</td><td>6 (30%)</td></tr>
<tr><td>Breast milk fortifier</td><td>5 (25%)</td></tr>
<tr><td>Formula</td><td></td></tr>
<tr><td>Use of EES</td><td>NA</td></tr>
</table>
HPS diagnosed at a median age of 4wks (2-7)

Median time range from onset of symptoms to diagnosis 10 (1-28) days

HPS was diagnosed by:
US 9
</td>
<td>First report on incidence of HPS in a large series of EA patients.

Previous reports were all small case series (total of 36 cases)

Incidence of HPS in EA is (7.5%) s 30 times higher than general population (0.25%)

Male predominance seen in EA-HPS too.

This study could not confirm other known associations for HPS:
First born, SGA, prematurity, birth in spring or summer , use of formula feeds or use of erythromycin

HPS should be considered in all EA patients with feeding intolerance and recurrent persistent vomiting despite being adequately treated for reflux</td>
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			Contrast study 4 Both 6 During surgical procedure 1	

Author/Year	Study Type	Patient 1	Patient 2	Conclusion
Michaud et al 2010	Case Series 2 patients with Dumping syndrome (DS)	Male VACTERL Type C EA, Primary repair with colostomy day 1 Feeding difficulties at 3months Feed refusal Weight 3.7kg (-3.25 SD) Length 56cms (-1.7SD) **Investigations:** Stools watery, +ve for reducing substance Stricture/HERD/esophagitis/SBBO/CMPI were excluded Intestinal transit time accelerated High BSL post prandially Abnormal glucose tolerance test: Early hyperglycemia and late hypoglycemia Insulin measurements were normal **Treatment** Uncooked starch before each meal during day and continuous feeds overnight Weight gain and growth normalized Uncooked starch stopped at 1yr when repeat glucose tolerance test was normal	Male Type C EA Primary anastomosis Day 1 Severe GERD treated with PPI + prokinetics 2 ALTE at 6 months 1 of these with seizures and low BSL, 2 hours after meal Failure to thrive Weight 5.1kg (-3SD) Length 65cms (-1.5SD) **Investigation** Abnormal glucose tolerance test with early hyperglycemia and late hypoglycemia Gastric emptying time was normal **Treatment** Uncooked starch with meals and continuous feeds overnight Fundoplication for GERD at 9months Uncooked starch ceased at 17 months. Overnight feeds ceased at 22 months At 3 years,4mths Weight 12.6kg (-1SD) Height 95cms (M)	Dumping syndrome can occur in EA without fundoplication It should be considered if EA patient presents with digestive symptoms, failure to thrive, malaise, refusal to eat. Other differential diagnosis in these patients include stricture, GERD, esophageal dysmotility, oral disorders DS can be confirmed with glucose tolerance test (early hyperglycemia and late hypoglycemia)

Author/Year	Study Type	Case	Conclusion
Tran et al 2011	Case report of EA with heterotopic gastric mucosa (HGM) in upper esophagus (Inlet patch)	Female Type C EA At 15 months-vomiting Contrast study showed stricture-dilated 24mths-vomiting and dysphagia No stricture on contrast but dysmotility and GER Fundoplication done as symptoms persisted despite PPI Gastrostomy closed at 31mths Surveillance gastroscopy at 6 yrs showed HGM At 7yr patient on normal diet with mild dysphagia	HGM has been reported in upto 34% of EA, but this is only second published case of HGM in EA HGM can present with dysphagia HGM diagnosed by endoscopy and biopsy HGM treated PPI +/-dilatation in past HGM should be considered in EA patients with ongoing feeding intolerance and dysphagia when other common causes like stricture and GERD have been excluded.

Other GI anomalies(apart from ano-rectal) associated with EA-TEF

Author/Year	Study type	Number of patients Patient characteristics	Results of Fecal Flora in EA-TEF	Conclusion
Bayston et al 1984	Prospective case series April 1981-April 1982	24 EA-TEF Anastomosis Primary 18 Delayed 4 Cervical esophagostomy 2 Feeding Gastrostomy 16 All fed within 48 hours TPN for 48-72 hours post op EBM+formula Oral feeding by 7th post op day 5 received antibiotics	Results from the 19 who did not get AB Staph Albus was the organism most frequently isolated. In a third of the pts it was the only organism isolated. By 2nd week Klebsiells, enterococci and clostridia were being isolated. By 3rd week Klebsiella was the commonest organism isolated Several species of Clostridia were isolated Semi quantitative assessment of bacterial numbers done in 3 pts: Staph Albus numbers increased over time Aerobic gram negative rods appeared in large numbers from the 1st day that they were detected When comparing with previous reports on fecal flora from healthy neonates (control): No Bifidobacteria were seen in EA-TEF in first week 2 babies still had no organism in stool by end of 1st week Only 1 had bacteroides compared to majority having it in controls The use of a gastrostomy rather than a trans-anastomotic feeding tube made no difference to the nature or time of appearance of the organisms No bacteria were isolated in 3/5 pts receiving AB. 4/5 became colonized with Candida	Bifidobacteria were absent in week one in EA-TEF unlike breast fed babies who show large numbers of these In EA-TEF Staph Albus predominated in 1st week. Anaerobic colonization was delayed and bacteroides were present in only 5 patients by week 3. Clostridia were present only in few patients in week 1. E. Coli did not appear before day 3 and Klebsiella was isolated from most only by end of week 3. The rate of intestinal colonization was slower in EA-TEF. The onset of intestinal colonization appeared to be temporarily related to enteral feeding. Vitamin K produced by enteric flora may not be available in EA-TEF babies at birth, hence may require additional dose at 2-3weeks of age if additional surgery is planned. Delay in colonization may have potentially deleterious effect on immunological development and ability to combat infections. Prophylactic antibiotics have deleterious effect on colonization and antibiotics should only be given for as short a period as possible when indicated.

Other GI anomalies(apart from ano-rectal) associated with EA-TEF

Author/Year	Study type	Number of patients Patient characteristics	Methods	Results	Conclusion
Halac et al 2012	Prospectively designed multicenter study Homogenous cohort of subjects	53 EA-TEF 25F Median age 12yrs (7.8-18) 72 Controls 34F Median age 13.4yrs (7.8-18.5) P=NS between groups	Primary outcome was prevalence of abdominal pain associated FGID (IBS, FD and FAP) according to Rome III criteria Secondary outcome was prevalence of chronic abdominal pain (once a wk for >8wks) Compare incidence of FGID in EA-TEF subjects with a complex neonatal history to patients from orthopedic clinics without complex neonatal history. To determine if complications and events following surgery in EA influenced long term development of abdominal pain related FGID in childhood. Exclusion criteria: IBD Gastroenteritis Abdominal surgery in previous 4 wks Intellectual disability Surgery for scoliosis Questionnaire of pediatric gastrointestinal symptoms (QPGS) that assesses symptoms associated with FGID in children and which has been adapted to Rome III criteria was used	EA-TEF 11/53 (21%) complained of FGID IBS 5 FAP 5 FD 1 Controls 8/72 (11%) FGID IBS 3 FAP 3 FD 2 OR for dev FGID in EA was 2.09 (95% CI 0.77-5.64, P>.05) No significant differences in symptom duration, intensity or limitation of activities between EA and controls with FGID None of the parameters (proxy for neonatal stress) of associated malformations, occurrence of post operative malformations, duration of intubation, age at oral feeding, duration of NICU or hospital stay were not a significant risk factor for the development of FGID in EA pts Chronic abdominal pain was present in 20/53 (38%) in EA vs 18/72 (25%) in controls, p>.05 Compared to controls EA had more dysphagia (49% vs 11%, p<.001), heartburn (25% vs 10%, p<.05) and regurgitations (23% vs 8%, p<.05)	Neonatal stress induced by EA repair was not a clinically significant risk factor for the subsequent development of pain associated FGID in later childhood. Subjects suffering from FGID had not been exposed to more severe neonatal stressful conditions

Transition to Adulthood, QOL and Barrett's in EA-TEF

Author/Year	Study Type	Number of Patients	Results	Conclusion
Deurloo et al (1) 2001	Case Report	1 Patient Caucasian male Type C EA Primary anastomosis Needed resection of anastomotic stricture at 18 months due to unsuccessful dilatations Asymptomatic post resection Occasional cigarette 4 units of alcohol daily	**At 38yr** **Symptom:** Dysphagia 4 Kg weight loss **Contrast study:** Irregular mid esophageal lesion with stenosis **CT Scan:** Mid esophageal lesion without metastasis **Endoscopy and biopsy:** **Squamous cell carcinoma** **Staging:** T3N0M0 **Treatment:** Chemotherapy Transthoracic subtotal esophsgectomy Post operative radiotherapy **Location of tumour:** 2cm distal to the scar of the anastomosis 2 years post surgery patients was well and tumour free	Potential for GER in EA to cause inflammation and stricture formation, especially at site of esophageal inflammation. The scar tissue could in the long term for esophageal squamous cell carcinoma. There is diminished peristalsis and slow clearance of the refluxate and food and saliva in the esophagus. This could predispose to esophageal squamous cell carcinoma. Any causal relationship between esophageal atresia and development of esophageal cancer cannot be unequivocally proven based on one case but this case makes one aware of a potentially increased incidence of esophageal cancer as the first generation of EA survivors reach middle aged adulthood

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Results	Conclusion
Sistonen et al (2) 2008	Case cohort study 1949-1978	502 EA patients treated during this period 88% had Type C EA 7.8% had Type A EA 2% had Type E EA 29 had gastric or colonic interposition No patient lost to follow up 230 died before 1967 younger than median age of 8days (1day-8.3yrs) These were excluded from analysis 272 remaining patients were eligible 142 males Median age at end of follow up 35yrs (2days-56yrs) **Methodology** Patients were followed up for cancer through the files of the population based countrywide Finnish cancer registry from 1967 to 2004 Number of cancer cases observed and person years at risk were counted and the expected number of caner cases estimated from the national cancer incidence rates There were 5 year age groups separately for both sexes and 4 calendar periods (1967-1976,1977-1985, 1986-1995, 1996-2004) Standardised incidence ratios (SIRs) were calculated by dividing the number of cancer cases observed by the expected numbers	**Table 1 shows number of patients operated on for EA and percentages of patients discharged alive by year of operation** **The number of person years at risk was 8034 (Table 2** **3 cases of cancer were seen vs 3.1 (expected, Table 3** These included 1 small intestinal lymphoma, 1 leukaemia and 1 carcinoma of uterus There were no cases of esophageal cancer, gastric cancer, lung cancer or laryngeal cancer	Absence of any case of esophageal cancer among the EA patients The crude incidence of esophageal cancer in Finland in 2003 was 4.3/100,000, with approximately 220 new cases annually Based on the upper 95% CI limit, **this study was able to exclude the long term risk of esophageal cancer after repair of EA 500 fold higher than that of the normal population** The overall cancer incidence among the EA patients did not differ from that of the general Finnish population This is the first epidemiological assessment of the occurrence of esophageal cancer among patients with EA As previous EA patients diagnosed with esophageal cancer were all relatively young, this was in the age range of this study cohort This is the only series of consecutive EA patients followed up for more than 50 years Given the young age of the oldest survivors, further studies and continued follow up are warranted to elucidate the risk for esophageal cancer and the need for endoscopic surveillance after repair of EA

Table 1 Number of patients operated on for EA in Finland and percentages of patients discharged from hospital alive by year of operation

Y	No. of patients	Survival (%)
1947-1956	100	19
1956-1960	100	43
1960-1965	101	56
1965-1971	101	70
1971-1978	100	85

Table 2 Person-years at risk among Finnish patients with EA in 1967 to 2004 by age and sex

Age (y)	Males (n = 142)	Females (n = 130)	All (N = 272)
0-14	1590	1312	2902
15-29	1831	1527	3358
30-44	905	732	1637
45-59	80	57	137
Total	4406	3628	8034

Table 3 Observed and expected numbers of all cancer cases and standardized incidence ratios (SIRs) with their 95% CI among Finnish patients with EA in 1967 to 2004

Age (y)	Observed	Expected	SIR	95% CI
0-14	-	0.4	0.0	0.0-9.4
15-29	1	0.9	1.1	0.0-6.1
30-44	2	1.4	1.4	0.2-5.0
45-59	-	0.4	0.0	0.0-8.8
Total	3	3.1	1.0	0.2-2.8

Author/Year	Study Type	Number of Patients Patient Characteristics	Result	Conclusion
Pultrum et al (3) 2005	Case Report	1 EA patient 33 week gestation BW 1590g Type C EA Primary repair under tension **Anastomotic complications:** Anastomotic leakage with mediastinitis Sliding diaphragmatic hernia **Symptoms:** Severe GER Recurrent stricture needing repeated dilatation Permanent double wire placed to with dilatations Persistent mild dysphagia Pyrosis Regurgitation Anorexia At 3yrs 3mths Height 92cm (p10-p25) Weight 11.87kg (<p10) **Investigations:** pH Metry: Reflux Index 50% Endoscopy showed erythema but not Barrett's **Treatment of GER** PPI Nissen Fundoplication at 16years Less frequent dilatations post fundoplication, last one at 19yrs	At 22years Weight loss Increasing dysphagia Endoscopy showed Barrett's with stenosis and irregular tissue at anastomosis Histology Highly differentiated adenocarcinoma Staging CT scan Endoscopic untrasonography T3N1M0 Treatment External and intraluminal radiotherapy Complication Bronchoesophageal fistula which needed stenting Patient died shortly thereafter	Second report of adenocarcinoma in EA patients Ongoing GER presumably led to Barrett's intestinal dysplasia and adenocarcinoma 22 years after primary repair In this patient GER in combination with mixed type sliding diaphragmatic hernia led to inflammation and worsening stricture formation at anastomotic site Not clear if any treatment of Barrett esophagus will have effect on natural course. Important to treat reflux aggressively and if symptoms persist or worsen endoscopy should be considered Authors conclude that it is still questionable to recommend long term follow up and cancer surveillance for all EA patients. But they state that GER should be treated reducing the dysplasia risk and subsequent adenocarcinoma of esophagus **Table 1 shows reported cases of esophageal carcinoma after EA repair in literature at time of this study**

Table 1 Reported cases of esophageal carcinoma after primary atresia repair, showing a younger age at presentation and the occurrence of gastroesophageal reflux in those with an adenocarcinoma

Reference	Age (y)	Histology	Stage	Strictures	Reflux
LaQuaglia et al [17]	44	Squamous cell carcinoma	T4 N0 M0	Yes	–
Adzick [18]	20	Adenocarcinoma	T2 N0 M0	Yes	Yes
Deurloo [19]	38	Squamous cell carcinoma	T3 N0 M0	Yes	–
This study (2005)	22	Adenocarcinoma	T3 N1 M1b	Yes	Yes

Transition to Adulthood, QOL and Barrett's in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics	Results	Conclusion
Alfaro et al (4) 2005	Case Report	1 EA Patient At age 6yrs had food impaction that required dilatation At age 20ors had dysphagia which was treated with dilatations GER symptoms for 5 years Did not drink or smoke	At age 46 years had increasing dysphagia Esophagoduodenoscopy showed Barrett's esophagus from 18-35cms and a friable mass in mid esophagus Dilatation done and biopsy taken Histology showed Barrett's esophagus with high grade dysplasia and focal carcinoma in situ Staging CT scan PET scan No metastatic disease seen Treatment Neo adjuvant chemo-radiation Blunt esophagectomy and gastric pull through and cervical anastomosis Patient on normal diet and well at 2 months follow up at time of study	Authors conclude that practitioners need to be aware of increased risk in EA patients of adenocarcinoma If dysplasia is seen in biopsies they need to treated aggressively Adults who had EA repair need to be reviewed and questioned about GER and dysphagia symptoms and enrolled in surveillance program consisting of either periodic endoscopy or UGI series

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Results of Questionnaire	Results of esophagoscopy (EGS) and histology	Conclusion
Deurloo et al (5) 2005	Prospective case cohort study	Between 1973-1985 123 EA patients were born 28 died 3 lost to follow up 92 patients 54 (53%)M 38 (41%)F Median BW 2610g (750-3880) Median gestational age 38wks (28-43) 42 (46%) had other congenital malformations Distribution of EA Types similar to other large studies In first year GERD diagnosed in 33 (36%) based on symptoms and/or pH Metry 19/33 (58%) had Boerema anterior gastropexy for failed medical treatment of GER 18/92 (20%) had stricture in first 3 years requiring 3 or more dilatations This was more frequent in GERD patients; 12/33 (36%) vs 6/59 (10%) p=.03 **Methodology** **Questionnaire (Table 2) sent to all patients** GERD defined as patients having symptoms of reflux or complications of reflux. Symptoms included heartburn, regurgitation and dysphagia In esophagoscopy macroscopic signs of esophagitis were described according to modified system of Savary Miller. Biopsies were taken as per ESPGHAN protocol Biopsies were judged for esophagitis and metaplasia as per Ismail Beigi et al Barrett's was defined as change in esophageal epithelium of any length that can be recognised at endoscopy and was confined to intestinal metaplasia	86/92 (94%) returned the completed questionnaire Median age of responders (which was equal to interval of follow up) was 17yrs (10-26) 36/86 (43%) had no complaints at all There was no age difference in symptoms Results of questionnaire shown in Table 2 23 complained of heartburn Swallowing solid food was a problem in one third (31) About half (39) needed fluids with meals 6 were under medical care for dysphagia or GERD 2 were on acid reducing medication	49/92 (53%) agreed to have esophagoscopy Biopsies were taken in 40/49 patients Patients who had EGS more likely to have complaints, 33/50 vs 16/36, p=.038 EGS showed no abnormalities in 34 (69%) Grade 1 in 11 (23%) Grade 3 in 2 (4%) Macroscopic lesion suggestive of Barrett's in 2 (4%) Hiatal hernia in 13 (30%) No biopsies taken in 9 because of normal appearing esophagus at EGS Histology showed no signs of esophagitis in 7/40 (18%) Reflux esophagitis in 30/40 (75%) Mild esophagitis 15 (38%) Moderate esophagitis 8 (20%) Severe esophagitis 3 (8%) No patients with intestinal metaplasia (Barrett's) 2 were on PPI at time of EGS Both had dysphagia 1 had heartburn In both EGS looked normal but histology showed severe esophagitis No correlation between complaints and results of EGS/histology **Table 3 shows results of histology in relation to results of EGS** **Anterior Gastropexy** This was done in 10/40 who had EGS 3 had heartburn/retrosternal pain Esophagitis found at EGS in 3/10 Macroscopic lesions suggestive of Barrett's seen in 2/10 Histologically proven esophagitis in 6/10 Gastric metaplasia in 3/10	Study re-establishes increased prevalence of esophagitis in EA patients, but no severe complications like peptic stricture or Barrett's was seen in this cohort. GERD symptoms were present in 33% Prevalence of GERD symptoms in the study group was higher than 18% in general adult population Dysphagia seen in 36%, but no strictures found EGS showed prevalence of esophagitis in 16%, assuming grade 1 esophagitis to be subjective and classified as normal. Based on histology esophagitis in 75%. Findings may be biased as more patients with complaints agreed to EGS. However even if all patients who did not have EGS had normal histology, the prevalence would still be 33% Results of EGS and histology in EA patients who had anterior gastropexy were disappointing. No correlation between complaints and endoscopic and histologic findings. Interestingly despite correlation between macroscopic EGS findings and histology in some patients in this study, 9 patients with normal EGS did not have biopsy Authors felt that study did not answer question whether long term follow up with EGS is worthwhile in EA patients, and how long it should be done. They felt that relatively short follow up (17.6yrs) in this study in addition to the low compliance in this cohort do not justify the performance of an EGS with biopsies at regular intervals. To do so further long term studies will be needed. The intended effect of EGS surveillance would be early detection of intestinal metaplasia and prevent development of esophageal malignancy.

Table 3 Relationship between findings at EGS and findings at histology

	Histology: esophagitis[a]				
	Absent	Mild	Moderate	Severe	Gastric metaplasia
Endoscopy					
Grade 0	5	12	6	3	0
Esophagitis[b]					
Grade 1	2	2	4	1	
Grade 2	1	1	0	0	0
Macroscopic image of Barrett esophagus	0	0	0	0	2

[a] Esophagitis scored according to Ismail-Beigi [14].

[b] Esophagitis scored according to the modified Savary-Miller [12] classification.

Author/Year	Study Type	Number of Patients Patient Characteristics	Results	Conclusion
Adzick et al (6) 1989	Case Report	1 patient Type C EA Primary anastomosis Had stricture which required several dilatations as an infant At 17 had hemi thyroidectomy for nodule (follicular carcinoma) Barium swallow done at that time showed abnormal motility in distal two thirds of esophagus. No GER or abnormality in lower esophagus seen	Age 20 developed increasing dysphagia 10lb weight loss Epigastric pain worse in post prandial period Barium swallow showed ragged intraluminal distal esophageal lesion Endoscopy showed irregular exophytic mass extending into esophageal lumen and distally into cardia Biopsy of lesion showed adenocarcinoma. No Barrett's proximal to tumour CT scan did not show metastasis Treatment Esophagectomy, colon interposition and pyloroplasty At 1 year follow up patient doing well without recurrence	First reported case of adenocarcinoma in the esophagus of an EA patient Although Barrett's was not seen histologically in this case, authors felt that the adenocarcinoma may have arisen in area of columnar epithelium lined esophagus which was obliterated by tumour Authors felt regular surveillance for chronic inflammation and dysplasia may be necessary in EA survivors. Vigilant life long follow up of these patients is important

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	GER	Results of pH Metry and Endoscopy and biopsy	Conclusion
Burjonrappa et al (7) 2011	Retrospective Review 1990-2009	51 EA Patients 28M 23F Mean Gestational age37weeks (31-41) **EA Types** Type A 5 Type C 44 Type D 1 Mean age at follow up 6.6years (7months-19years) **Methodology** Contrast study day post repair All on anti reflux treatment Duration of medication use determined by pH Metry or impedance study at age 1year Endoscopy done at 3yrs and every 3 years thereafter until 18yrs Biopsies done at endoscopy Mild GER treated with acid reducing medication and/or prokinetics Severe GER treated with fundoplication Surveillance endoscopy and biopsy continued every 3 yrs post fundoplication Barrett's defined as presence of intestinal metaplasia (IM) Reflux index >4.2% considered abnormal in pH Study	37 (72.5%) had symptoms of GER Symptoms: Failure to thrive Dysphagia Anemia Respiratory issues Aspiration **EA Types in patients with GER** 100% in EA Type A (6) 70% in Type C EA (31) 100% in Type D (D) **Fundoplication** Done in 17/37 (46.5%) 6 had reflux induced mucosal abnormality (RIMA) despite fundoplication (1 Collis, 1 Toupet, 4 Nissen) Median age 7 months (3months-4years) Patient with Barrett's had 2 fundoplication Patient with GM had 1 fundoplication Fundoplication did not prevent development of metaplasia later 6 with RIMA were treated with maximal medical treatment and annual endoscopy No ablative treatment for metaplasia Regression of GM in 1 11 who had fundoplication at median age of 21 months (4months-5years) did not develop RIMA 2 had wrap failure **Stricture** Seen in 22 18/37 with GER (about 50%) had dilatation for strictures vs 4/14 without GER who had dilatations and only in 1st yr of life (p=NS) Only 10 were weaned off acid suppressive treatment 41 were on treatment at last follow up	**pH Metry** 33 had pH Metry 21 (64%) had Reflux Index >4.2% **Endoscopy** 38 had endoscopy 15 (39.5%) had mucosal abnormalities 11/15 had Gastric Metaplasia (age 2-16yr) 1/15 had Intestinal Metaplasia,15 yr. 2/15 had Grade A Esophagitis(5-15yr) 2/15 had Grade D esophagitis (ulcerative esophagitis) (4-9yrs) Both patients with Grade D had gastric Metaplasia 2/15 had Eosinophilic Esophagitis (6-8yrs) 1 with EoE had Gastric Metaplasia (6yrs) Total of 12 (23.5%) had GM or IM Mean age of patients with metaplasia was 13yrs. This was significantly different from that of patents without metaplasia (5.2yrs), p<.001 **Other endoscopic findings:** 2 had tight fundoplication wrap 1 diverticulum at level of anastomosis 1 hiatal hernia 12 had pH Metry alone 17 had endoscopy only **Concordance between studies in 13 patients** **Discordance in 8 patients** Concordance for positive reflux studies in 6 patients Concordance for negative reflux studies in 7, p=.349 **Discordant studies (Table 2):** 6 had normal endoscopy with a reflux index of >4.2% (4.8-17.3) 1 had GM and negative pH study 1 had negative pH study post fundoplication but had GM	72.5% had endoscopic or pH probe confirmed GER Fundoplication in 33% Barrett's (IM) seen in 2% Authors advocate close follow up of all EA patients to evaluate for RIMA irrespective of symptoms The frequency, intensity and methodology of screening in asymptomatic children is controversial In this study although there was no significant discordance between pH study and endoscopy there were patients who were detected by pH study and not by endoscopy and those that had metaplasia and not by pH Metry Negative endoscopy after abnormal pH study could be due to treatment of reflux which can prevent RIMA 2 with abnormal endoscopy and normal pH study, 1 had prior fundoplication and other had GM. The patient GM could have been due to pulled up stomach pH probe and endoscopy are complimentary. Authors advocate pH study to detect all patients with GER and later endoscopy allows detection of ongoing GER and it's complication Treatment of GER is important to reduce stricture formation. Patients without GER had fewer dilatations and only in first year of life compared to those with GER Mean age at last follow up for those with GM was 13yrs this was significantly different to those without metaplasia (5.2yrs), p<.001 The lag time to the development of metaplasia from initial time of EA repair was about 10 years Hence early teen years is when intensive screening should begin

					As Barrett's (IM) and GM can persist despite fundoplication and optimal medical treatment, surveillance of these patients should continue. Authors did endoscopy every 3 years in those with metaplasia but no dysplasia, every 6 months for low grade dysplasia with intervals between endoscopies to be increased if IM improved or stays stable on treatment. High grade dysplasia should be treated with surgical resection of the esophagus or photodynamic therapy therapy of the mucosa at specialized centres

Table 2 Clinical features of patients with discrepancy between endoscopy and pH probe studies.

Type of atresia	pH probe findings	Endoscopy findings	Comments/Medication
type C	reflux index 17.3%	normal mucosa	had recurrent fistula at 1 year and dilatation of multiple stenosis; PPI
type C	reflux index 6.1%	normal	stenosis dilated once; PPI and prokinetic
type C	normal	gastric metaplasia	PPI, recurrent laryngitis
type C	reflux index 6.6%	normal	on PPI and prokinetic
type A	normal	gastric metaplasia	dilated multiple times. Had Nissen fundoplication at 7 months. Gastric metaplasia likely pulled up fundus? PPI
type C	reflux index 4.8%	normal	dilated multiple times. PPI
type C	reflux index 15.9%	normal	PPI
type C	reflux index 11.5%	normal	dilated multiple times. Nissen at 2 years. PPI

PPI: proton pump inhibitor

Author/Year	Study Type	Number of Patients Patient Characteristics	Results of Esophagojejunal anastomosis and total esophagogastric disconnection (TED)	Conclusion
Gottrand M et al (8) 2013	Retrospective Review 1999-2013	244 had EA repair 12 had total esophagogastric disconnection (TED) 5 in EA patients Severe GERD 3 Microgastria + GERD 1 Severe esophageal dysmotility 1 6 in neurologically impaired patients 1 in patient with laryngeal diastema EA Types in Patients who had complications post TED Type A 1 type C EA 3 Long Gap EA 2 2 had fundoplication prior to TED 2 had gastrojejunal feeds prior to fundoplication	**4/5 EA patients who had TED had complications:** Esophagojejunal anastomotic stricture3/4, 5months -9 years after TED Barrett's esophagus with Gastric Metaplasia in3/4, 8-9 years after TED Combined esophagojejunal anastomotic stricture and gastric metaplasia 2/4 Dumping Syndrome in 1 **Symptoms of complications:** Feeding difficulties Dysphagia Salivary stasis Vomiting Food impaction 1 patient with Esophagojejunal stricture treated with endoscopic dilatation with Savary Gillard bougies over 2 years and Mitomycin C application on 2 occasions 1 with esophagojejunal anastomotic stricture was treated with Savary Gillard bougie dilatation subsequently developed gastric metaplasia and dysphagia which improved spontaneously over time 1 with Combined esophagojejunal anastomotic stricture treated with balloon dilatation and improved subsequently developed GM and increasing dysphagia. Improved on PPI	First study to describe esophagojejunal anastomotic stricture and gastric dysplasia as long term complications of TED Systematic follow up with endoscopy helps in the diagnosis of metaplasia and strictures in TED patients, the symptoms of which are not specific and can be absent or mild or related to EA itself (dysmotility) Dysphagia in EA patients with TED could be due to dysmotility, stricture, feeding disorder, dumping Reason for esophagojejunal stricture is not clear as there was no anastomotic leakage or mediastinitis at time of TED. Severe GERD prior to TED with abnormalities in distal esophageal mucosa or bile reflux may play a role, although Rous en y makes latter less likely. Regarding Barrett's post TED, GM might have been present at time of TED, or remnant gastric mucosa might have been conserved at time of TED, although these patients had endoscopy prior to TED which did not show Barrett's and only 1 patient had cardiac type Barretts Results warrant long term follow up into adulthood of every EA patient having TED, and decision for endoscopy cannot be based on symptomatology. Patients with gastric metaplasia are at high risk for later development of dysplasia and cancer and would benefit from life long endoscopic surveillance Barrett esophagus and esophagojejunal anastomotic stenosis are a cause of feeding disorders in patients with TED

Transition to Adulthood, QOL and Barrett's in EA-TEF

Author/Year	GERD and Barrett's Esophagus (BE) in Esophageal Atresia (EA)
Hassall (9) 2011 Review Article	**GERD in EA** Esophageal Dysmotility Poor clearance of refluxate Hiatal Hernia "Silent Reflux" lack of complaints by patient All these contribute to complications of reflux in EA patients **Definition of BE** Consensus studies in adults and children now include cardia type epithelium in definition of BE The term "Endoscopically suspected esophageal metaplasia" is (ESEM) s recommended. When biopsies of ESEM show columnar epithelium the diagnosis is BE, and the presence or absence of IM (intestinal metaplasia) is stated **Prevalence of BE in EA** Unreliable data in studies due to small number Lack of uniform diagnostic definitions Lack of adherence to process of care criteria for diagnosis Screening only symptomatic patients will miss some BE Australian study by Andrew Taylor et al (2007) showed prevalence of 11%. Although this study had standardised protocol for landmark identification, endoscopy was done in only 62/485 EA patients and probably represents under diagnosis of BE for reasons of acquisition (only symptomatic patients were endoscoped) and exclusion of metaplasia other than intestinal **Management of BE in EA** Treatment of non dysplastic BE is the same as treatment of GERD Presence of BE does not mandate fundoplication **Indication for fundoplication in BE is the same as for GERD:** Failure of optimised medical treatment Poor compliance Pulmonary aspiration High dose twice a day treatment with PPI monitored against esophageal pH study is indicated High dose PPI might slow the development of dysplasia or reduce the risk of adenocarcinoma There is no evidence that surgery does this any better than medical treatment **Endoscopic evaluation in EA** To evaluate cause of symptoms To determine whether metaplasia is present and what type it is To rule out dysplasia Symptomatic patients should undergo evaluation regardless of age Symptoms or their absence is not predictive of erosive esophagitis or Barrett's metaplasia **Time line from no dysplasia to high grade dysplasia appears to be at least 3-5 years** Youngest patients with adenocarcinoma of esophagus is 10 years old Logical to screen EA patients at age 10yrs regardless of symptoms If they are on acid suppressive medication, initial endoscopy should be done on treatment Landmarks should be documented Staining of biopsies with Alcian blue pH 2.5 should be done If erosive esophagitis is present or landmarks are unclear, endoscopy should be repeated 3-4 months later on high dose PPI For Barretts with or without IM repeat endoscopy is recommended only in 3-5 years unless new symptoms develop For BE with dysplasia the management options as adults apply

Author/Year	Study Type	Number of Patients Patient Characteristics	Results	Conclusion
LaQuaglia et al (10) 1987	Case Report	1 patient 45 year old white female Type C EA Long Gap Ante grade thoracic food conduit begun at 11 months and finished after 40 operations over 1.5 years Discharged home on normal diet at 2.5yrs Skin tube extended from cervical esophagostomy to a Roux en Y loop of jejunum brought across costal margin At 10yrs had pain, induration and erythema of proximal limb which responded to antibiotics	At age 45 complained of dysphagia Did not use alcohol or smoke Erythema, induration and hyperpigmentation over proximal limb Barium swallow showed polypoid mucosal irregularity along proximal limb of skin tube. Second sessile filling defect distally Endoscopy showed inflammation of neoesophagus and distal polyp Polyp removed and 15 biopsies taken Polyp showed pseudoepitheliomatous hyperplasia. Mucosal biopsies surprisingly showed esophageal mucosa rather than epidermis Due to persistent symptoms patient had resection of skin tube and retrosternal coloesopagoplasty. Roux en Y was taken down and anastomosis of colon to stomach done in addition to pyloroplasty.. Antral web resected. Discharged on normal diet Resected conduit showed areas of well differentiated squamous cell carcinoma No metastasis on workup Patient develop recurrent SCC and radical excision done and post operative radiation started.	First case of Squamous cell carcinoma (SCC) in ante thoracic skin tube esophageal conduit in EA patient in English literature European literature (Linder et al)showed 12 previous cases in non EA patients Sapozhnikova reported 2 cases of SCC in 13 patients who had conduit. Petru had 1 case of SCC in conduit. Diagnosis of malignancy in mucosal biopsies difficult in the skin conduits due to thickening of basement membrane. In current case 15 biopsies were negative and SCC was shown only in resected specimen. Interval of 3 decades (31.2+/- 6.2years) in Linder's and 31.5+/-4 yrs in Sapozhnikova's series between creation of skin tube and development of carcinoma. Papilloma formation may also be seen. Causes of malignancy include thermal, chemical, mechanical and GERD Development of SCC is a late complication of ante thoracic skin tube esophageal conduit in place for several decades. Their use in benign disease in younger patients with long life expectancies including EA patients should be avoided. If a conduit is used long term follow up is required. Development of inflammation or pseudoepitheliomatous hyperplasia endoscopically or radiographically may signal malignant degeneration. As endoscopic biopsy may miss malignancy, removal of conduit is indicated in presence of gross inflammatory changes, polyp formation or unexplained induration or thickening.

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Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Results	Conclusion
Faugli et al (11) 2009	Case cohort study 1999-2002	44 EA Patients 2 died Mothers of 2 could not speak Norwegian These were excluded 39/40 Mothers (97.5%) agreed to participate 27M 12F Median age 13 months (12-18) 9 born prematurely Only 1 with BW <1500g Primary anastomosis in 35 Delayed anastomosis 4 (1-3months). These had gastrostomy with suctioning of upper pouch every 10min and post repair they had anastomotic leak 20(51%) had feeding difficulties including dysphagia, GER, choking, feed refusal, food impaction **Clinical characteristics, Medical condition and environmental variables at 1 year of age are shown in Table 1** **Methodology** **Assessment of Infant Psychopathology Assessed by Diagnostic Classification DC 0-3** Infant mental health was related to primary disorders (Axis 1) and relationship disorders (Axis II) **Quality of mother infant relationship assessed with Parent-Infant Relationship Global Assessment Scale (PIR-GAS),** <40 was "disordered", 40-79 was "at risk" and >79 was at "adapted" mother child relationship **Eating behaviour** disorder characterized by food refusal was sub classified into infantile anorexia, sensory food aversions, post traumatic feeding disorder or feeding disorder associated with mental conditions **A clinical child psychiatric assessment based on "Infant and Toddler Mental Status Exam**" was done **Assessment of infant development done using "Bayley Scale of Infant Development" (BSID-II):** >115 was "accelerated performance", 85-114 was "within normal limits", 70-84 was "mildly delayed performance, and 69 and below was "significantly delayed performance **"Infant Temperament was done using "Infant Behaviour Questionnaire" (IBQ).** Positivity reactivity scale and Negativity reactivity scale were used in analysis	36 (92%) completed the developmental assessment with a mean Mental Index (BSID-II) of 103 (71-118) 4 had mildly delayed mental performance (70-84) Same 4 also showed significantly delayed psychomotor performance (</=69) 21 mothers (54%) reported that their child had experienced trauma 12 had observed post traumatic symptoms All traumatic events related to medical conditions and treatment procedures Majority of families had no or slight family difficulties **Infant mental health outcomes shown in Table 2** 12 (31%) had disorders according to DC 0-3 10 (26%) were on Axis I and 4 (11%) on Axis II 2 on both Axes Traumatic Stress Disorder 3 Eating behaviour disorder 3 Regulatory disorder 3 Disorders of affect 3 Mixed relationship disorder 3 Under involved relationship disorder 1 **Table 3 shows univariate logistic regression analysis to look for associations between child, medical and environmental variables and psychopathology** Girls were more likely to have mental health disorders (OR 4.9, p=.033) Having post traumatic symptoms increased risk of psychopathology 6.2 times, p=.018 Gastrostomy increased risk of psychopathology 26 times, p=.005 Severe feeding difficulties and prolonged mechanical ventilation increase risk 6.2 times, p=.018 More than 1 operation increased risk 5.7 times, p=.021 A CFD score of at least 4 increased risk for child psychopathology 7 times, p=.011 at 1yr and was the only independent prognostic environmental variable that predicted psychopathology **Multiple regression analysis also shown in Table 3** Post traumatic symptoms remained significant with OR 5.2 Having >1 operation (p=.035) and mechanical ventilation >1 day (p=.031) were independent prognostic medical variables predicting psychopathology	Psychopathology was identified in infants with EA Mental disorders were found in almost one third (31%) of infants with EA at 1 year of age 60% of the primary mental disorders found (Traumatic stress disorder and PTFD) were related to long term effects of traumatic experiences connected to clinical symptoms or to treatment procedures All 3 children with "Eating Behaviour Disorder" were classified as PTFD Severity of medical condition, invasive treatment procedures and family strain were related to mental health disorder More than 1 operation, >1 day mechanical ventilation and moderate/severe family strain predicted psychopathology Parent child relationship disorder was seen in 11% and represented one third of diagnosed psychopathology A non optimal relationship (PIR-GAS40-79) was identified in n additional 37% of the mother child dyads. These dyads were characterised by under involved/over anxious mothers EA infants needing prolonged mechanical ventilation and repeated surgical interventions experienced a less optimal caring situation than did other EA infants Traumatised mothers of these infants are emotionally and functionally unavailable for their children and PTSD in mothers is an important predictor of the child's trauma response This the first study to examine mental disorders in a group of EA infants. The strength of the study is the assessment for DC:0-3 diagnosis via observation as well as use of a checklist Study suggests that relational trauma, vulnerable attachment and impaired self development as possible pathways to mental disorders following hospitalisation in infants and young children Small patient numbers is a study limitation Authors state that EA infants at increased risk for a mental health disorder should be identified and special attention given to the infant's emotional development if the infant suffers from post traumatic symptoms, if ventilation needed >1 day or >1 operation is needed. Early intervention and family support important in these infants

		Maternal Mental Health was assessed by General Health Questionnaire (GHQ 30) **Maternal anxiety was assessed by the Spielberger State Anxiety Inventory (STAI X-1 and 2)** Clinically important strait anxiety if STAI X-2 was at least 40 **Family Strain was assessed using "Chronic Family Difficulties" (CFD),** where 0 was none and 6 very severe. Chronic if difficulties lasted at least 1 year and were present at follow up		

TABLE 1. *Clinical Characteristics, Medical Condition, and Environmental Variables of 27 Boys and 12 Girls With Esophageal Atresia at 1 Year of Age*

Clinical characteristics of the child	
Birth weight (g), *Mdn* (range)	2,830 (595–4,570)
Prematurely born (<37 weeks), *n*	9 (23%)
Mental index (BSID-II), *M* (range)	103 (71–118)
Psychomotor index (BSID-II), *M* (range)	97 (56–121)
Traumatic experience reported by mother, *n*	21 (54%)
Posttraumatic symptoms, *n*	12
Medical condition/treatment	
Longest hospital stay (days), *Mdn* (range)	21 (13–270)
Total admissions, *Mdn* (range)	3 (1–38)
Total no. of operations, *Mdn* (range)	1 (1–5)
Mechanical ventilation >1 day	12
Severe feeding difficulties, *n*	11 (28%)
Gastrostomy, *n*	7
Dilatations of esophagus, *n*	8
No. of dilatations/patients requiring dilatation, *Mdn* (range)	7 (2–55)
Antireflux surgery, *n*	2
Environment	
Maternal age (years), *M* (range)	31 (25–44)
Maternal education (years), *M* (range)	14 (9–29)
Maternal psychological distress (Total GHQ-30), *Mdn* (range)	20 (8–52)
Maternal well-being (GHQ-30), *Mdn* (range)	1.00 (.25–1.50)
Maternal state anxiety "case" (STAI X-1), *n*	6 (16%)
Maternal trait anxiety "case" (STAI X-2), *n*	14 (38%)
No. of children in the family, *Mdn* (range)	1 (1–5)
Chronic Family Difficulties, *Mdn* (range)	2 (0–6)

BSID-II = Bayley Scale of Infant Development; GHQ-30 = General Health Questionnaire; STAI X-1 = Spielberger State Trait Anxiety Inventory (12-item version); STAI X-2 = Spielberger State Trait Anxiety Inventory (20-item subscale).

TABLE 2. *Diagnostic Classification of Mental Health (DC: 0–3) of 39[a] 1-Year-Old Infants With Esophageal Atresia*

Diagnostic classification: 0–3	*n*
Axis I: Primary Disorders	
Traumatic Stress Disorder	3
Disorders of Affect	1
Regulatory Disorders	3
Eating Behavior Disorder	3
Total no. with primary diagnosis	10 (26%)
PIR-GAS[a] (mother–infant)	
>79	20 (52%)
40–79	14 (37%)
<40	4 (11%)
Axis II: Relationship Disorder[a] (mother–infant)	
Underinvolved	1
Mixed	3
Total no. with relationship disorder[a]	4 (11%)
Total no. with DC: 0–3 Axis I or Axis II diagnosis	12 (31%)[b]

PIR-GAS = Parent–Infant Relationship Global Assessment Scale.
[a]One infant was followed to the observation by the father, thus PIR-GAS and Axis II was determined on 38 mother–infant dyads.
[b]Two cases had diagnoses on both axes.

TABLE 3. *Unadjusted and Adjusted Odd Ratios for Psychopathology Among Children With Esophageal Atresia at 1 Year of Age (The Reference Category Is Given in Parentheses in Column 1.)*

	Univariate logistic regression Odds ratio (unadjusted)		Multiple logistic regression Odds ratio (adjusted)	
Child	(95% confidence interval)	*p*	(95% confidence interval)	**p**
Gender (male)	4.9 (1.1–21.2)	.033*	4.0 (.84–19.2)	.082
Birth weight (>2,500 g)	1.0 (.20–4.55)	.951		
Mental Developmental Index (Bayley Scales) (continuous)	.941 (.886–1.0)	.051		
Psychomotoric Developmental Index (Bayley Scales) (continuous)	.968 (.921–1.0)	.197		
Positive reactivity (IBQ) (continuous)	.868 (.06–1.2)	.390		
Negative reactivity (IBQ) (continuous)	.777 (.41–1.5)	.435		
Posttraumatic symptoms (no)	6.2 (1.4–27.7)	.018*	5.2 (1.1–25.1)	.041*
Medical condition/treatment				
Longest hospital stay (<22 days)	4.0 (.95–16.9)	.060		
Severe feeding difficulties (no)	6.2 (1.4–27.7)	.018*		
Delayed anastomoses (no)	8.7 (.80–94.3)	.076		
Gastrostomy (no)	26.0 (2.6–258.2)	.005*		
Operation >1 (no)	5.7 (1.3–25.0)	.021*	5.7 (1.1–28.3)	.035*
Mechanical ventilation >1 day (no)	6.2 (1.4–27.7)	.018*	6.1 (1.2–31.5)	.031*
Environment				
Chronic family difficulties (none to moderate)	7.0 (1.6–31.5)	.011*		

*$p < .05$.

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Physical Functioning	Cognitive and Psychosocial Functioning	Family Functioning and Psychosocial Stressors	Conclusion
Bouman et al (12) 1999	Case cohort study	41 eligible children and parents 36/41 (87.8%) participated Mothers and fathers of 36 children completed the questionnaire 29 children completed psychological testing and questionnaire 20M 16F Mean 10.2years (8-12) Demographic and Medical Characteristics shown in Table 1 Associated minor congenital anomalies 14 Associated major congenital anomalies 11 Methodology IQ tested with 2 sub tests, Vocabulary and Block design of the Wechsler Intelligence Scale for children (WISC-RN) which together have a correlation of 0.92 with full scale IQ Children completed the Self Perception Profile for Children (SPPC) a 36 item questionnaire for 8-12yr old children Children also completed the abbreviated Depression Questionnaire for Children (ADQC) a 9 item questionnaire Parents completed the Child Behaviour Checklist (CBCL) to assess behavioural and emotional problems of children Teachers of the children completed the Teacher's Report Form (TRF) which is a teacher version of the CBCL Family functioning was assessed with the General Functioning Scale of the Family Assessment Device (FAD)-a 60 item family questionnaire Psychosocial stress in the family was measured with the Life Events Questionnaire (LEQ)	Parents reported good health for most of children 16 had excellent outcomes with no feeding, swallowing or respiratory problems 9 had good outcome with slight feeding or respiratory problems'4 had fair outcomes with moderate feeding problems and recurrent respiratory problems 6 had physical problems due to associated congenital abnormalities	Results of cognitive and psychosocial functioning shown in Tables 3 and 4 The mean IQ was 90.2 which is 10 points lower than the standardised normal score of 100, p<.01 8 (22%) required special education vs 4% in the general population, p<.001 Mean IQ of children in Montreal class I was 14 points lower than those in class II, p<.05 Twice as many children as in normal population showed increased rates of emotional and behavioural problems as reported by parents as well as teachers Mothers and teachers reported more internalizing problems 31% and 37% in the deviant range, p<.001 Fathers reported more externalizing problems 29% in the deviant range, p<.020 No differences in the parent reported problem behaviour between the children in the different Montreal classes Half the children in Montreal class II were reported by teachers to have elevated levels of emotional and behavioural problems although there was no significant difference between Montreal class I and II Children with lower IQ scores showed more problem at school, with correlation between IQ and TRF, r=-.45,p<.05 Children reported no higher rates of depression or lower self esteem compared to normative data Children with lower IQ had more feelings of depression, correlation between IQ and ADQC,r=-.70,p<.001and lower school competence, correlation between IQ and SPPC,r=.38,p<.05	Mean total score on the FAD was similar to the mean score and SD in Dutch normative sample Level of psychosocial stress in the family in the year before assessment was not higher than the general population Higher rates of parent and child reported behavioural and emotional problems were reported for children in worse functioning families (correlation between FAD and CBCL total problem score r=.37, p<.05; correlation between FAD and ADQC r=.47, p<.01) and for children with higher rates of psychosocial stress in the previous year (correlation between LEQ and CBCL total problem score r=.49,p<.01)	10% of children had moderate swallowing and respiratory problems directly related to EA 15% had physical problems associated with other congenital anomalies especially anorectal malformations First follow up study of children with EA in which the psychosocial and social functioning of the children was investigated using a broad range of standardized assessment procedures of parents and children Children with EA had considerably lower IQ scores than children in the general population and their participation in special education was 5 times as frequent as in the general population In those with major congenital anomalies the mean IQ was more than 20points lower than the norm (77.6). whereas the mean IQ of the low risk children was in the normal range (94.8) Lower IQ correlated with higher rates of self reported depression and moderately correlated with rates of teacher reported emotional and behavioural problems Montreal classification not only has a role in predicting mortality but is also a prognostic indicator of long term cognitive problems in children with EA Children with EA had significantly more emotional and behavioural problems as reported by parents and teachers compared to general population. Children themselves did not report more feelings of depression or lower self esteem Neither presence of associated congenital anomalies or length of hospitalisation or number of operations were related to current

				Higher rates of present physical problems as reported by children were associated with lower scores on SPPC on 2 scales (General Self Worth r=-.43,p<.05 and Physical Appearance r=-.49 p<.01) No child was being treated in a mental health service		psychosocial functioning Children with more current physical problems showed less self worth and negative perception of physical appearance It is likely that rather than a specific anomaly having a congenital anomaly is a risk factor for psychosocial problems There was normal family functioning and no increased levels of psychosocial stress The whole EA group is at risk for increased learning, emotional and behavioural problems. Those EA patients with associated congenital anomalies are at risk for later intellectual problems More attention needs to be paid to the psychosocial and social functioning of EA children during their development and when problems are identified interventions should be planned

Table 1. Demographic and Medical Characteristics

Characteristics	
Age	8-12 yr (mean, 10.2)
Sex ratio	20 boys, 16 girls
SES*	
Low SES	5
Middle SES	18
High SES	13
Type of Esophageal atresia	
EA with tracheoesophageal fistula	31
EA without fistula	5
Duration of first hospital stay	13-690 d (median, 58.5 d)
Operations to follow-up	1-9 (median, 3)
Esophageal dilatations	0-32 (median, 1.5)
Montreal Classification	
Low-risk class I	28
High-risk class II	8

*Socioeconomic status based on the highest occupational level in the family.[16]

Table 3. Mean IQ Scores and Mean Scores on Questionnaires Concerning Psychosocial Functioning Versus Normal Scores for the Whole Group and Mean Scores of Montreal Class I Versus Montreal Class II

Outcome	Normal Score	Esophageal Atresia (n = 36)	Montreal Class I (n – 28)	Montreal Class II (n – 8)
WISC-RN	100	90.3 (16)†	93.5 (13.9)	79.4 (19.6)*
CBCL total problems	21.19	23.0 (19.7)	22.7 (18.5)	24.0 (25.6)
TRF total problems	19.50	23.3 (22.5)	20.7 (20.7)	33.7 (28.0)
General self-worth	3.28	3.47 (.49)	3.4 (.49)	3.6 (.47)
Scholastic competence	2.80	3.01 (.67)*	3.0 (.67)	3.0 (.72)
Depression	1.73	1.34 (1.9)	1.0 (1.3)	2.6 (3.0)
Family functioning	20.1	19.0 (4.33)	18.9 (4.1)	19.0 (5.4)
Psychosocial stress	1.50	1.46 (1.5)	1.5 (1.5)	1.2 (1.6)

Note: Mean scores were compared with normal scores using one-sample *t* tests and scores of Montreal class I were compared with Montreal class II using independent samples *t* tests.

*$P < .05$.

†$P < .01$.

Table 4. Proportion of Deviant Scores for IQ, CBCL, and TRF and Proportion in Special Education for Whole Group and Montreal Class I Versus Montreal Class II

Outcome	Whole Group (%) (n = 36)	Montreal Class (%) I (n = 28)	Montreal Class (%) II (n = 8)
IQ	30*	26.1	42.9
Special education	22‡	21.4	25.0
CBCL			
Total problems	28.6*	28.6	28.6
Internalizing	22.9	21.4	28.6
Externalizing	20.0	21.4	14.3
TRF			
Total problems	34.5†	30.4	50.0
Internalizing	37.9‡	34.8	50.0
Externalizing	20.7	13.0	50.0*

Note: Proportions with deviant scores were compared with proportions in general population using nonparametric binomial tests. Proportions in general population: IQ, 15% <85; special education, 4%; CBCL and TRF, 14.5% in deviant range.

*$P < .05$.

†$P < .01$.

‡$P < .001$.

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Results of Health Related Quality Of Life	Conclusion
Peetsold et al (13) 2010	Case cohort study 1988-1997	84 EA patients treated during this period 18 patients excluded 66 EA patients included **Methodology** 31 were at or below 13yrs and their parents were invited to complete the CHQ-PF50 Parents of 24 completed it (77%) There was no significant differences in age at follow up, type of EA, associated anomalies, fundoplication between respondents and non respondents of CHQ-PF50 Patient characteristics are shown in Table 2 20 had Type C EA 1 Type A 1 Type B 2 Type E GORD was confirmed by endoscopy and or pH Metry and contrast series in 6 63 were 10yrs or older and were invited to complete the CHQ-CH87 37 (58%) completed it No significant difference in age at follow up, type of EA, associated anomalies, fundoplication between respondents and non respondents of CHQ-CH87 33 had Type C EA 1 Type B 2 Type E GORD was confirmed by endoscopy and or pH Metry and contrast series in 14 GI symptoms were scored according to Manterola (Table 1). Patients scoring 4b or more were suspected of GORD Health related quality of life (HR-QOL) This was assessed using CHQ-PF50 for parents of children </=13yrs and CHQ-CF87 for children >/=10yrs Results of CHQ PF%) were compared with norm scores based on representative sample of 353 Dutch school children aged 5-13yrs and the results of CHQ CF87 were compared with norm scores based on sample of 475 Dutch adolescents using the unpaired t test All questionnaires were mailed out. Parents and	**Questionnaires** **CHQ-PF50** Parents of 24 EA patients completed it In most domains the scores were similar to the reference population **(Table 3)** Moderate to large effect sizes for General Health Perceptions and the Physical Summary Scale respectively (Table 3) **CHQ-CF87** 37 patients completed it In most domains scores were similar to healthy reference population EA patients scored significantly better in the Family Activities scale, p=.02 and significantly lower on General Health Perception,p=.01 although effect sizes were small **(Table 4)** **Factors influencing HR QOL outcomes** **CHQ-PF50** Multivariate analysis showed only associated anomalies and age at follow up were independent determinants of General Health. 1 concomitant anomaly decreases General Health by 15.36 points and 2 or more decrease it by 30.72 points In regression analysis when age at follow up increases by 1 year the Physical Summary scale decreases by 3.05 points (Table 5) **CHQ-CF87** Only General Health Perception was significantly lower in EA patients This domain decreased by 3.54 points for every point the child scores on the Manterola reflux questionnaire after adjustment for tracheomalacia and presence of concomitant anomalies **(Table 6).**	First study to measure health related QOL following correction of EA in children aged 6-18yrs. In most domains HR QOL in EA patients was comparable with healthy controls. This might be because of willingness of parents and patients to accept symptoms and as they have had them their whole life not apprehend their limitations. Parents as well as children reported lower scores for general health perception, which was negatively influenced by presence concomitant anomalies. This reflects not only presence of serious illness but that the parents and child perceive their current health as suboptimal and are worried about future. Children reported their general health perception being influenced by GER symptoms. Significantly lower physical summary scores reported by parents which was independent of concomitant anomalies and reflux symptoms Surprisingly older age negatively affects HR-QOL. This could be because children were only in their adolescence to expect improvement of EA symptoms and HR-QOL Parents reported a lower mental health, indicating children were more anxious/depressed. However no relationship between mental health and respiratory or GER symptoms was found. Children themselves reported a normal mental health. Family activities had a high score but small effect size as reported by children, indicating they did not feel their health was a source of tension for the family and might even strengthen family relationships. Many patients still experienced GI symptoms like dysphagia. Non significant differences from normal were found in physical functioning, role functioning emotional (parent) and general behaviour (child) suggesting EA does affect HR-QOL in several domains in childhood. More than half of children in secondary school

		children completed the questionnaire independently		participated in highest educational level. This could be because of a selection bias as highly educated parents are more likely to participate in follow up study. Parental and children's self-reports provide different outlook on HR-QOL and are complementary. Study limitation was low rate of participants although there was no significant difference between participants and non participants in age at follow up and clinical parameters nothing was known about the current health of the non participants. Health care workers need to be aware of high incidence of symptoms and negative consequences for general health in EA patients. These patients need long term follow up.

Table 1 Scale and score of the reflux questionnaire according to Manterola et al. (19)

Item	Frequency	Score
Heartburn	Daily	3
	At least once per week	2
	At least once per month	1
	Never	1
Regurgitation	Daily	3
	At least once per week	2
	At least once per month	1
	Never	0
Dysphagia	Yes	1
	No	0
Chest pain	Permanent	2
	Occasionally	1
	Never	0
Nocturnal cough	Permanent	2
	Occasionally	1
	Never	0
Dysphonia	Yes	1
	No	0
Asthma	Yes	1
	No	0

Table 2 Patient characteristics

	CHQ-PF50 n = 24	CHQ-CF87 n = 37
Male	16 (67%)	21 (57%)
EA type C	20 (83%)	33 (89%)
Concomitant anomalies	11 (46%)	16 (43%)
GORD	6 (25%)	14 (38%)
Antireflux surgery	6 (25%)	10 (27%)
LOS (median days)	15.0	17.0
Follow-up		
Age (mean ± SD; range)	11.3 ± 1.2 (9–13 years)	14.0 ± 2.4 (10–18 years)
Pulmonary medication	4/21 (19%)	6/30 (20%)
Primary school	12/21 (57%)	6/30 (20%)
Very good/good exercise tolerance	17/21 (81%)	23/30 (77%)
Sport practice (x/week; mean ± sd)	2.9 ± 1.3	2.3 ± 1.6
Current tracheamalacia	14/21 (67%)	19/30 (63%)
Wheezing	5/21 (24%)	9/30 (30%)
Feeding difficulties	10/21 (48%)	13/30 (43%)
Manterola score (mean ± SD)	2.6 ± 2.3	2.3 ± 2.3

Table 3 Results of the CHQ-PF50

	EA patients n = 24	Reference population* n = 353	95% CI of the difference	Effect size
Physical Functioning	92.8 (15)	99.1 (4.3)	−12.78–0.23	0.41
Role Functioning Emotional	93.5 (12.2)	97.9 (7.2)	−9.54–0.78	0.36
Role Functioning Physical	91.0 (15.5)	95.8 (15.6)	−11.38–1.73	0.31
Bodily Pain	80.9 (18.3)	85.7 (17.2)	−12.75–3.09	0.26
General Behaviour	77.4 (14.2)	78.5 (13.1)	−7.26–5.04	0.08
Mental Health	76.3 (11.5)	81.4 (12.1)	−10.02–−0.28	0.43
Self-Esteem	79.2 (14.6)	79.2 (11.0)	−6.22–6.15	0
General Health Perceptions	62.3 (25.1)	82.9 (13.4)	−31.19–−9.96	0.82
Parental Impact Emotional	81.3 (20.5)	86.3 (15.2)	−13.69–3.59	0.25
Parental Impact Time	92.6 (15.9)	94.0 (13.0)	−8.14–5.32	0.09
Family Activities	86.3 (16.1)	91.5 (11.9)	−12.03–1.60	0.32
Family Cohesion	73.1 (17.7)	72.2 (19.4)	−6.54–8.39	0.05
Physical Summary Score	50.0 (9.1)	56.4 (5.7)	−10.33–−2.44	0.70
Psychosocial Summary Score	52.3 (8.4)	53.2 (6.4)	−4.53–2.69	0.11

Data are expressed as mean (SD).

*Reference values according to Raat et al. (22).

Table 4 Results of the CHQ-CF87

	EA patients n = 37	Reference population* n = 475	95% CI of the difference	Effect size
Physical Functioning	95.7 (6.6)	96.0 (6.9)	−2.51–1.90	0.04
Role Social Limitations Emotional/Behavioural	92.2 (14.0)	89.4 (17.2)	−1.88–7.46	−0.16
Role Functioning Physical	94.3 (15.2)	95.0 (12.9)	−5.77–4.36	0.05
Bodily Pain	72.4 (25.9)	73.5 (22.7)	−9.69–7.56	0.04
General Behaviour	77.7 (10.2)	80.9 (10.6)	−6.59–0.20	0.30
Mental Health	77.4 (14.7)	76.5 (15.4)	−4.00–5.81	−0.06
Self-Esteem	73.0 (13.1)	74.7 (12.2)	−6.05–2.69	0.13
General Health Perception	64.8 (19.4)	73.5 (16.5)	−15.13–−2.19	0.45
Family Activities	86.0 (14.5)	80.0 (17.7)	0.96–10.95	−0.34
Family Cohesion	71.4 (19.7)	70.6 (23.5)	−5.86–7.44	−0.03

Numbers are expressed as mean (SD).
*Reference values according to Raat et al. (23).

Table 5 Results of the univariate and the multivariate analysis of CHQ-PF50 domains

	Univariate analysis						Multivariate analysis	
	Mental Health		General Health		PhysSS		General Health	
	B	p	B	p	B	p	B	p
Age at follow-up (years)	−3.47	0.07	−7.28	0.08	−2.58	0.09	−8.18	0.03
Concomitant anomalies	−4.68	0.14	−14.12	0.04	−1.57	0.54	−15.36	0.02
LOS	0.02	0.62	−0.02	0.82	−0.03	0.32		
Antireflux surgery	−2.78	0.62	−6.99	0.57	−6.70	0.13		
Feeding difficulties	−4.64	0.39	−17.51	0.12	−2.39	0.58		
Manterola score	−1.09	0.33	−2.63	0.26	−1.16	0.18		

Table 6 Results of the univariate and the multivariate analysis of CHQ-CF87 domain General Health

	Univariate analysis		Multivariate analysis	
	B	p	B	p
Age (years)	−1.33	0.33		
LOS (days)	−0.22	0.14		
Congenital anomalies	−10.00	0.02	−8.37	0.09
Antireflux surgery	−8.83	0.22		
Tracheamalacia	−17.58	0.02	−12.68	0.07
Feeding difficulties	−4.05	0.60		
Manterola score	−4.02	0.02	−3.55	0.03

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Symptoms and Functional Tests after Colon Interposition in EA	Quality of Life after Colon Interposition in EA	Conclusion
Ure et al (14) 1995	Case cohort study 1963-1971	146 EA patients Colon interposition done in 9 (6.2%) 8M 1F Mean weight 3081g (2000-4100) Mean height 51.5cm (46-56) EA Types (Vogt) Type II 3 Type IIIa 1 Type IIIb 5 Associated malformation 2 Mean age at esophageal replacement 15.1months (5-32) 10 colon interpositions done Transverse colon iso peristaltically in 4, anti peristaltically in 2 Right colon iso peristaltically in 1 and anti peristaltically in 3 All except 1 had retro sternal reconstruction Mean number of operations 4.2 (3-8)/child Mean duration of hospital stay 20.2months (11-42) 6 had uneventful course 2 had leakage 1 died from sepsis Mean age at follow up 24yrs (19-27) Mean body weight 64kg (60-69) Mean height 174cm (168-179) **Methodology** **Standardised questionnaire** Eating and swallowing and side effects evaluated according to criteria of DeMeester Clinical examinaltion Ultrasound Blood tests for FBC,iron, albumin **Functional Study** Fluoroscipically measured transit time for liquid barium (20ml) and bite of barium burger Ability to consume standard meal of 824 calories assessed according to method of De Meester 3 had endoscopy with biopsy and manometry **QOL** 3 instruments Global QOL assessed by visual	5 working full time 1 student 2 married with children **Blood tests** FBC, iron, albumin, protein all normal **Ultrasound** normal in all 3 graded result very good, 4 good, no bad or very bad **Results for eating habits, swallowing ability and side effects of operation shown in Table 2** **Barium study** Time for first liquid barium to reach stomach was 1-9 minutes compared to <10 seconds in healthy controls In all some liquid barium was entrapped for >4min in colon graft after swallow In 1 reached stomach >15min **Manometry** 3 had it In none were colonic contractions or peristaltic movements in the colon related to swallowing was recorded Peristaltic wave stopped at esophago-colic anastomosis **Endoscopy** Normal esophageal, colonic, ileal and gastric mucosa Severe elongation of graft in all No reflux colitis	Unimpaired QOL as indicated by the Spitzer Index 8-10 points in all except 1, mean 9 (SD 2.4) On 100 point **Visual Analogue Scale** patients scored Global Quality of Life mean 66 (SD 18), which indicates significant impairment, **Table 3** Mean GIQLI was 92.2 (SD 26.5) This was significantly less than 107.6 (SD 18.7) in 150 healthy individuals, p=.02 **Patients suffered from GI symptoms frequently, Figure 3** Symptoms scored 49.3 in patients compared to 59 in healthy volunteers, p=.02 No significant differences for physical functions, social functions, emotions and inconvenience for medical treatment between patients and controls	Unlike other studies where retrosternal colonic interposition was done where there was a high complication rate of leakage, stricture formation, acid reflux, respiratory infections, anaemia and diarrhoea in this study apart from leakage in 2 in early post operative period there were no long term complications Normal colonic mucosa on biopsy after mean of 22 years on endoscopy Delayed esophageal transit time and colonic redundancy. No colonic peristalsis in relation to swallowing seen. No metabolic abnormalities seen on blood tests There was considerable impairment of QOL using a unidimensional scale but no impairment using Spitzer Index, but Spitzer Index was set up for cancer patients and does not look at specific symptoms. In contrast in GIQLI there was significant impairment of QOL, exclusively due to specific symptoms. Authors concluded that after colonic interposition EA patients apart from specific symptoms may lead an otherwise normal life. However long term follow up is recommended especially to look for diverticular disease and carcinoma.

		analogue scale Spitzer index Gastrointestinal quality of life GIQLI			

Transition to Adulthood, QOL and Barrett's in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Symptoms	Quality of Life	Conclusion
Ure et al (15) 1998	Case Cohort Study 1963-1971	146 children operated on for EA Primary anastomosis done in 137 (93.8%) 63/146 (46%) survived Mean age at primary anastomosis 1.7days (0-6) 1 with EA Vogt Type II had delayed anastomosis at 5 months In 9 (6.2%) had colon interposition for long gap 8/9 (88.9%) survived Mean age at colon interposition was 15.1 months (5-32) **50 with primary anastomosis and 8 with colon interposition were seen (Table 1)** 58 (81.7%) had follow up Mean age at follow up was 25.3years (20-31) **Methodology** **Symptoms Assessment** Standardised questionnaire focussed on gastrointestinal and pulmonary symptoms. Eating habits, swallowing ability and long term side effects of operation were evaluated according to criteria of DeMeester et al Physical examination Results of operation scored by patients and parents as: A. very good result/no complaints B. Moderate result/symptoms that the patient is willing to tolerate C. Poor result/therapy indicated **Assessment of Quality of Life** 3 Instruments Global quality of life as determined by visual analogue scale Spitzer Index Gastrointestinal quality of life GIQLI For comparison GIQLI of 150 healthy individuals from Eypaschs etal study was used	Primary anastomosis (50) Meal capacity unrestricted in 46 (92%) 24 (48%) suffered from "hold up" some of the time 12 (24%) had diarrhoea 11 (22%) had heartburn Other GI symptoms in <20% each Respiratory symptoms seen frequently 30 (60%) recidivating cough and bouts of bronchitis 15 (30%) short of breath some of the time Colon interposition Gastrointestinal symptoms were frequent 5 (62.5%) had "hold up" 5 had diarrhoea All had shortness of breath, in 5 this was present all the time Unrestricted meal capacity in 3 (37.5%)	After primary anastomosis 40 (80%) were working full time 7 (14%) were students 3 (6%) unemployed 17 (34%) married 13 (26%) had children After colon interposition 5 (62%) working full time 2 married with children 1 student 2 working in institution for handicapped **Global QOL score, Spitzer Index and GIQLI were higher in primary anastomosis group compared to those with colonic interposition (Table 2)** Difference in Global Quality of Life did not reach significance Spitzer Index 9.7 in primary anastomosis was significantly higher than in colonic interposition 8.8, p<.05 GIQLI in primary anastomosis similar to healthy controls GIQLI in primary anastomosis significantly lower than in colonic interposition, p<.0001 and compared to healthy controls, p<.05 Breakdown on GIQLI showed significant difference for symptoms. Symptoms scored 49.3 (SD 10) after colon interposition compared with 61.7 (SD 4.7) after primary anastomosis, p<.0001 and vs 54.8 (SD 5) in healthy controls, p<.05 No significant differences found for physical functions, social functions, emotions, inconvenience of medical treatment between primary anastomosis, colon interposition and healthy controls Result of operation classified as poor in 1 due to persistent stricture which was dilated by bougie All other patients had "optimal" result or were tolerating symptoms without further therapy	60% after primary anastomosis had respiratory symptoms Most frequent GI symptom was "hold up", which was seen in 48% 22% had GER symptoms such as heartburn or regurgitation Only a minority had symptoms most of the time Patients with primary anastomosis had unimpaired QOL The global QOL scored 80-100 points which was similar to normal individuals. The Spitzer Index was optimal and the GIQLI was similar to healthy volunteers. Neither GI nor respiratory symptoms had relevant impact on QOL and were not major GI symptoms and SOB were more frequent in colon interposition compared to primary anastomosis. The Spitzer Index and GIQLI were also significantly lower in colon interposition group in colon interposition group compared to primary anastomosis and healthy volunteers Impairment in GIQLI was caused by specific symptoms and had no impact on physical functions, emotions and social functions. Therefore long term QOL after colon interposition was acceptable in this study Survival rate of 43% was similar to other studies from 1960-70 period. However as survival nowadays is around 95%, the favourable results of analysis from this study may not count and long term QOL remains to be reinvestigated

Table 1. Characteristics of 58 Patients Who Underwent Follow-Up After Esophageal Atresia

	Primary Anastomosis (n = 50)	Colon Interposition (n = 8)
Male/female (n)	22/28	7/1
Birth weight (mean)	2,666 g	3,081 g
Associated malformations (n)		
Imperforate anus	4	—
Duodenal atresia	1	—
Cardial	2	1
Renal	2	—
Skeletal	13	1
Other	7	—
Type of atresia according to Vogt[7] (n)		
Type I	—	—
Type II	1	2
Type IIIa	—	1
Type IIIb	48	5
Type IIIc	1	—
Follow-up data		
Age (mean)	26.3 yr	24 yr
Body weight (mean)	64 kg	63 kg
Hight (mean)	168 cm	174 cm
Thoracal circumference (mean)	91 cm	90 cm

Table 2. Quality of Life After Esophageal Atresia

Method of Evaluation	Primary Anastomosis (n = 50) Mean (SD)	Colon Interposition (n = 8) Mean (SD)	Healthy Controls (n = 150) Mean (SD)
Visual Analogue Scale[11]			
(0-100 points)	80.1 (18.6)	67.5 (18)	—
Spitzer Index[12] (0-10 points)	9.7 (0.8)	8.8 (2.1)*	—
Gastrointestinal Quality of Life Index GIQLI[13-15]			
(0-128 points)	111.5 (8)	92.2 (26.5)†	107.6 (18.7)
Classification of the outcome[10] (n)			
A. Very good	36 (72%)	3 (37.5%)	—
B. Moderate	13 (26%)	5 (62.5%)	—
C. Poor	1 (2%)	—	—

*$P < .05$ versus primary anastomosis.

†$P < .0001$ versus primary anastomosis and $P < .05$ versus healthy controls.

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Results of Developmental Assessment	Conclusion
Walker et al (16) 2013	Prospective case cohort study 2006-2008	34 EA infants 3 excluded (death, extreme prematurity and chromosomal anomaly) 3 pure EA 1 Type E EA 27 Type C EA Primary extrapleural repair by postero lateral thoracotomy Gastrostomy in LG EA No routine dilatations All commenced on Ranitidine postoperatively 62 Control infants No significant difference between gestational age between EA-TEF (37.7wks) and controls (38.1) or between their BW (2718g, SD+/-717g) 8 of the EA-TEF group were prem Majority 62.5% were female and singleton pregnancies (94%) Median length of stay in hospital was 19days (8-134) 14 (44%) had associated congenital anomalies **Methodology** Data sourced from the Development after Infant Surgery (DAISy) study Healthy controls from co-located maternity units enrolled contemporaneously over the period of the EA-TEF children and were matched 2for 1 by gestational age **Infants assessed at a corrected age of 1 year using the Bayley Scales of Infant and Toddler Development Version III (BSITD III)** 5 scales Cognition Receptive Language Expressive Language Fine Motor Gross Motor Mild developmental delay >-2SD—1SD Moderate delay <-3SD—2SD Severe delay </=-3SD below the mean Each infant assessed by 2 Bailey trained assessors one of whom was blinded to the infants study group Mean scores for infants with EA-TEF on the 5 subscales were compared to the control infants	Infants with EA-TEF scored significantly lower on one of the sub sales of the BSITD III They scored lower on the expressive language subscale compared to healthy controls, p<.05 In all subscales there was a small difference in the mean with the EA-TEF infants scoring lower than the normal infants **(Tables 2 and 3)**	This is one of the first prospective studies to compare the developmental outcomes at 1 year of age in infants with EA-TEF with a cohort of healthy infants using the standardised norms of BSITD III Children with EA-TEF had significantly lower scores in the expressive language subtest at 12 months corrected, and in addition there was a non significant difference in the other subscales too Although the EA-TEF cohort had a significantly lower score in the expressive language subscale compared to healthy controls their mean score was still within the average range for the assessment Although the gross motor sub scores were not significantly different in the EA-TEF group, 39% of them had evidence of delay in gross motor skills compared to 21% of control infants, with the majority of the delay classified as mild. The lack of statistical significance in the other sub scales could be due to small sample size Another study limitation is the fact that the EA-TEF cohort has had only 1 developmental assessment done at early age of 1 year. But authors plan to reassess the cohort at 3 years to ascertain developmental progress Results of this study is important as it highlights early identification of children at risk of poor neurodevelopmental outcome the importance of the application of early intervention services to ensure optimal outcome in these children. Authors feel that it is important to enrol EA-TEF patients in developmental follow up clinics

Table 2 Summary of developmental assessment

Bayley-III domain	Group	Mean	*P* value
Cognition	Controls 62	11.69	NS
	OA/TOF 31	11.00	
Receptive language	Controls 62	10.94	NS
	OA/TOF 31	10.23	
Expressive language	Controls 62	10.06	$P < 0.05$
	OA/TOF 31	9.03	
Fine motor	Controls 62	10.05	NS
	OA/TOF 31	9.16	
Gross motor	Controls 62	9.27	NS
	†OA/TOF 30	8.37	

†One infant was in a plaster cast and gross motor was not assessed. NS, not significant; OA, oesophageal atresia; TOF, trachea-oesophageal fistula.

Table 3 Categorisation of delay

Bayley-III domain	Delay	OA/TOF ($n = 31$)	Control ($n = 62$)
Cognition	Mild	1	2
	Moderate	0	0
	Severe	0	0
	Total *n* (%)	1 (3%)	2 (3%)
Receptive language	Mild	7	11
	Moderate	0	1
	Severe	0	0
	Total	7 (23%)	12 (18%)
Expressive language	Mild	5	8
	Moderate	1	0
	Severe	0	0
	Total	6 (19%)	8 (13%)
Fine motor	Mild	4	5
	Moderate	0	0
	Severe	0	0
	Total	4 (13%)	5 (8%)
Gross motor	Mild	8	12
	Moderate	3	1
	Severe	1	0
	Total	12/(39%)†	13 (21%)

†One infant was in a plaster cast and gross motor was not assessed. OA, oesophageal atresia; TOF, trachea-oesophageal fistula.

Transition to Adulthood, QOL and Barrett's in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Results of Quality of Life	Conclusion
Deurloo et al (17) 2005	Case Cohort Study 1947-1986	227 EA patients treated Patients >16yrs included 134 survivors 15 excluded Remaining 119 **Methodology** Long gap defined as Type A or B EA Non long gap Type C, D or E EA **QOL Instruments used** **Generic QOL** **The Medical Outcome Study 36 item Short Form Health Survey (SF-36)** The 8 domains aggregated to a Physical Component and Mental Component Summary Scale Positive Affect measured by Positive Affect Scale **Disease specific QOL** **The Gastrointestinal Quality of Life Index GIQLI** **Modified Esophageal Cancer Module Questionnaire (EORTC-OES24)** **Illness Cognition Questionnaire (ICQ)** **3 Open ended questions** 1. Anything patients wanted to do but could not do because of past treatment or EA 2. 2. Whether EA had negative consequences on their life 3. 3. Whether EA had positive consequences on their life	97/119 (82%) response rate **The sociodemographic and clinical characteristics of the responders shown in Table 1** Women (91%) responded more than men (75%), p=.02 No significant difference in age, EA Type, presence or absence of associated anomalies between responders and non responders **Results of SF 36 and reference values shown in Table 2** **Generic QOL** EA patients scored significantly lower than healthy subjects on the general health scale and vitality scale Comparison between subgroups of patients Comparison between LG and non LG could not be made as there were only 4 LG patients **Table 3 shows results from patients with and without concomitant congenital anomalies** Those with anomalies scored significantly lower on the indigestion scale in EORTC-OES24 There were no significant differences amongst the various subgroups of anomalies **Open ended questions** **Question 1** 8 (8%) stated there were things they could not do because of EA These patients had a significantly lower score on overall physical functioning (SF 36), physical well being (GIQLI), total score in GIQLI and acceptation (ICQ). They had significantly higher score on helplessness (ICQ) **Question 2** 32 (33%) stated EA had negative impact on their life Dysphagia (22/32 69%) was mentioned most often Tiredness (6/32 19%) Scars (3/32 9%) These patients had a significantly lower score on the overall physical functioning (SF36), Physical well being (GIQLI), gastrointestinal symptoms (GIQLI) and total score of GIQLI	Study with good response rate (82%) which measured QOL following EA correction in 97 (16-48yrs) patients No differences in overall physical and mental health between EA patients and healthy subjects EA patients reported worse general health and less vitality than healthy subjects Quarter had GI problems (dysphagia) Most patients were either employed and had finished high school (77%) or were in school full time (31%) Marital and family status did not differ from general Dutch population Presence of concomitant congenital anomalies did not seen to affect the QOL, although, patients with concomitant congenital anomalies (35%) reported a lower QOL in the domain of indigestion (EORTC-OES24) Exploratory questions showed only a small number of patients felt limited because of EA (8%) However 34% experienced negative consequences of EA due to GI symptoms. These patients perceived their QOL to be impaired. Similarly patients with positive consequences due to EA scored higher on disease benefits domain Limitation: no information on health of non responders Parents of newborns with EA can be reassured that the long term outlook for their children with regard to their QOL is good

			Question 3 14 (14%) had positive consequences from their EA Positive outlook on life (7/14 50%) These patients had a significantly lower score on the domains of physical role (SF 36) and acceptation (ICQ) They had significantly higher score on domain disease benefits (ICQ)	

Table 1. Sociodemographic and Clinical Characteristics of the Responding Group (n = 97)

Characteristic	Finding*
Age, mean ± SD, y (range)	26.8 ± 7.9 (16.3-48.2)
Sex	
Male	55 (57)
Female	42 (43)
Marital status	
Married/living with partner	34 (35)
Unmarried/divorced/living alone	16 (16)
Living with others (eg, parents)	47 (49)
Children	
None	75 (77)
Yes, healthy	20 (21)
Yes, not healthy (1 child with tracheoesophageal fistula; 1 child with myocarditis)	2 (2)
Education	
Primary school	6 (6)
High school	44 (45)
Further education	36 (40)
University	9 (9)
Occupation	
Paid function	66 (68)
Unpaid function	9 (9)
Student	30 (31)
Unemployed	4 (4)
Type of atresia	
Long-gap atresia (type A or B)†	4 (4)
Non–long-gap atresia (type C, D, or E)†	93 (96)
Concomitant congenital anomalies	
None	63 (65)
Present	34 (35)
Anorectal malformations	11 (11)
Cardiac malformations	17 (18)
Renal malformations	9 (9)
Limb malformations	2 (2)
Other malformations	14 (14)

*Values are number (percentage) unless otherwise indicated.
†Type of atresia according to Gross classification.[10]

Table 2. Results of the SF-36 in Responding Patients and the Reference Group

Scores	Esophageal Atresia Group, Mean (SD), No. (n = 97)	Reference Group, Mean (SD), No. (n = 607)[16]	*P* Value
SF-36			
Physical functioning	91 (15)	95 (8)	.03
Physical role-functioning	92 (23)	91 (22)	.62
Emotional role-functioning	91 (25)	90 (26)	.39
Bodily pain	88 (18)	85 (17)	.10
General health	76 (21)	82 (13)	.008
Vitality	51 (14)	75 (15)	<.001
Social functioning	92 (16)	91 (16)	.53
Mental health	82 (14)	82 (14)	.81
SF-36 component summaries			
Physical component summary	54 (7)	55 (5)	.24
Mental component summary	49 (7)	51 (8)	.05

Abbreviation: SF-36, Medical Outcome Study 36-Item Short-Form Health Survey.

Table 3. Results of the SF-36, Positive Affect Scale, GIQLI, EORTC-OES24, and Illness Cognition Questionnaire

Scores	Concomitant Congenital Anomalies: Yes, Mean (SD), No. (n = 34)	Concomitant Congenital Anomalies: No, Mean (SD), No. (n = 63)	*P* Value
SF-36			
Physical functioning	89 (18)	93 (14)	.33
Physical role-functioning	93 (21)	92 (24)	.76
Emotional role-functioning	92 (22)	91 (27)	.79
Bodily pain	88 (16)	88 (18)	.92
General health	79 (21)	75 (21)	.30
Vitality	52 (13)	51 (14)	.57
Social functioning	91 (17)	93 (16)	.59
Mental health	84 (12)	82 (14)	.53
SF-36 summaries			
Physical component summary	54 (7)	54 (7)	.96
Mental component summary	50 (7)	49 (8)	.72
Positive Affect Scale	75 (18)	71 (19)	.29
GIQLI			
Physical well-being	24 (3)	23 (4)	.07
Gastrointestinal symptoms	68 (8)	68 (6)	.93
Total score	129 (12)	127 (12)	.71
EORTC-OES24			
Indigestion scale	4 (9)	12 (17)	.01
Single items			
Dry mouth	6 (13)	6 (17)	.97
Troublesome taste	2 (8)	2 (8)	.90
Troublesome coughing	10 (19)	13 (23)	.48
Troublesome talking	0	3 (9)	.09
Illness Cognition Questionnaire			
Helplessness	7 (3)	7 (1)	.19
Acceptation	22 (3)	22 (2)	.96
Disease benefits	14 (6)	12 (5)	.09

Abbreviations: EORTC-OES24, European Organisation for Research and Treatment of Cancer Esophageal Cancer Module; GIQLI, Gastrointestinal Quality of Life Index; SF-36, Medical Outcome Study 36-Item Short-Form Health Survey.

Transition to Adulthood, QOL and Barrett's in EA-TEF

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Results of Quality of Life after Gastric Transposition in EA Patients	Conclusion
Ludman et al (18) 2003	Case cohort Study	28 Patients 18M 10F Mean age 12.99+/-5.59years (2-22) All had gastric transposition (GT) **Methodology** **Patients divided into 2 groups** **Group 1 (13)** **Had cervical esophagostomy and gastrostomy No attempt was made to anastomose the esophagus** 4 Type C EA 6 Type A EA 3 Type B EA **Group 2 (15)** **Had undergone previous attempts at esophageal reconstruction** including 6 replacements (4 colon, 2 Scharli) 4 Recurrent TEF 4 Fundoplication 1 chronic leak 1 anastomotic disruption and extreme FTT **QOL Measures** **Gastrointestinal Quality of Life (GIQLI)** Modified and 9 new esophageal specific items added For those 2-4yrs old items in GIQLI which were inappropriate were excluded	Mean time since GT was 10.11years (SD 6.23) (0.84-19.53) Number of operations mean 24+/-22 (2-91) Patient characteristics shown in Table 1 4 (2 in each group) were below school age 8 (3 in group 1 and 5 in group 2) had left school 1 in university, 3 in college, 3 employed 5 in school age were in special unit or special schools (9/17, 53%) 2 of older patients in special unit 2 had moderate learning difficulties (13/28, 46%) Apart from 1 all were living with parents **QOL outcomes** **Patient Response** N=19 (10-22years) Total mean QOL was 122 (SD 14), range 94-141 **Disease specific subscale score higher in group 1 compared to group 2 (Table 3)** **Number of patients reporting symptoms and side effects shown in Table 4 and 5** No relationship between total QOL scores, associated anomalies, gender and number of operations since GT or time since GT **Parent Responses** Patients aged 9-18years, n=17 The total mean score based on parental perception was 117 (SD 21), range 74-144 **Patients in group 1 had higher score than those in group 2, Table 6** For patients in group 1, the fewer post GT procedures the patient underwent the higher the parental rating of QOL,p=.025 No association between these variables in group 2,p=.84 No association in either group between parental assessment of QOL and their gender or length of time since GT **Agreement between patients and parents** 13 parent and patient pairs, 7 in group 1 and 6 in group 2 completed GIQLI In group 1 6/7 parents rated their child's QOL higher than the patients themselves In group 2,5/6 patients perceived their QOL as being better than their parents perceptions	No other study has looked at medium term outcome for EA patients requiring gastric transposition (GT) Patients with EA who had GT as the primary reconstructive procedure experienced fewer disease specific symptoms in the medium term compared to patients who had undergone previous unsuccessful attempts at reconstruction Overall QOL of both groups of patients excluding young patients was generally unimpaired by any side effects of GT However direct comparisons with validation study of the GIQLI (25-60yrs) cannot be made as questionnaire was modified to include esophageal symptoms. However the mean score in Group 1 124 was similar to healthy subjects (125.8) Whereas Group 2 (119) was outside the 95% CI Lower proportion of patients in who had GT as primary procedure (Group 1) experienced dysphagia (30% vs 67%) or pain after eating (20% vs 33%) compared to patients who had undergone previous unsuccessful attempts at reconstruction of their esophagus (Group 2) Smaller proportion of patients in Group 1 had GER symptoms of heartburn or regurgitation compared to those in Group 2 (40% vs 67%) Some breathless during day was experienced by more than half of patients in both groups but breathlessness at night was more frequent in Group 2 Differences between both groups was not related to length of time since GT Patients in Group 1 experienced fewer disease specific symptoms such as dysphagia, dumping and pain after eating With exception of psychological and physical/social symptoms, parents in Group 1 perceived the health related QOL of their children to be significantly better than parents of patients in Group 2 Overall QOL of young children (2-4yrs) in Group 2 was adversely affected by eating difficulties compared to Group 1 50% vs 33% had dysphagia 50% vs 67% pain after eating

			Parent Response **Patients aged 2-4years, n=5** The overall QOL mean score was 87+/-20, range 61-108 Group 1 (n=2) 81+/-6 (77,85) Group 2 92+/-27 (61-108), n=3 Physical Growth Apart from 1 patient in each group all were below 50th centile for weight 5 in group 1 (41%) and 2 (12%) in group 2 were above 50th centile for height All had BMI z scores below 0 (-0.10—3.91)	33% in both groups had GER symptoms Similar proportion had breathlessness during day in both groups 44% had associated anomalies which affected their lives With 1 exception all patients and families were extremely satisfied with outcome of GT Patients led normal lives but were less socially and emotionally independent than their peers

Table 1. Patients' Characteristics

	Group 1 (n = 13) Mean (SD)	Group 2 (n = 15) Mean (SD)
Age (yr)	13 (5)	13 (6)
Gestational age (wk)	36 (3.4)	35 (3)
Body weight (kg)	2.14 (.54)	2.39 (.89)
Number of patients (%) with associated anomalies	9 (69)	8 (53)
Age at GT (decimal yr)*	0.95 (0.6)	4.56 (5)
Time since GT (decimal yr)	12.26 (5.34)	8 (7)
Total No. of all operative procedures*	14 (15)	32 (25)
Related to oesophagus before transposition	1	19 (21)
Related to oesophagus after transposition	2 (2)	5 (7)
Body mass index: weight (kg)/length $(m)^2$ (z scores adjusted for age and sex)	−1.67 (0.98)	−1.70 (1.10)

*$P < .05$.

Table 3. Quality of Life: Patient Responses

	Group 1 (n = 10) Mean (SD)	Group 2 (n = 9) Mean (SD)	95% CI for Difference
Aspects of eating (0-16)	12 (2)	12 (3)	−1.95, 2.64
Disease specific (0-84)	77 (6)	72 (10)	−3.34, 12.47
Psychological (0-20)	16 (2)	16 (3)	−2.66, 2.17
Physical/social (0-24)	19 (5)	19 (4)	−4.69, 4.86
Total (0-144)	124 (13)	119 (17)	−9.44, 18.95

Table 4. Patient Reported Symptoms: Eating Habits and Swallowing Ability

	Group 1 (n = 10) No. (%)	Group 2 (n = 9) No. (%)
Unrestricted diet	6 (60)	4 (44)
Size of meals similar to family/peers	4 (40)	2 (20)
Liquids with meals similar to family/peers	3 (30)	4 (44)
Slow eating	4 (40)	3 (33)
Dysphagia	3 (30)	6 (67)
Number meals per day	Median 5 (1-5)	Median 4.5 (2-6)

Table 5. Patient Reported Side Effects of Gastric Transposition

	Group 1 (n = 10) No. (%)	Group 2 (n = 9) No. (%)
Regurgitation	2 (20)	5 (56)
Heartburn	3 (30)	2 (22)
Vomiting	2 (20)	2 (22)
Halitosis	2 (20)	3 (33)
Dumping symptoms (diarrhoea, sweating, dizzy)	4 (40)	6 (67)
Respiratory tract infections	2 (20)	2 (22)
Breathlessness	6* (60)	5 (56)

*One (10%) breathless at night versus 3 (33%) in group 2.

Table 6. Quality of Life: Parent Responses

	Group 1 (n = 8) Mean (SD)	Group 2 (n = 9) Mean (SD)	95% CI for Difference	*P* Value
Aspects of eating (score 0-16)	13 (4)	10 (3)	.122, 7.30	.044
Disease specific (score 0-84)	76 (9)	64 (12)	1.10, 22.26	.033
Psychological (score 0-20)	17 (4)	15 (4)	−1.89, 5.59	.311
Physical/social (score 0-24)	21 (5)	15 (6)	−.094, 10.65	.054
Total (0-144)	127 (18)	104 (19)	3.37, 41.63	.024

Author/Year	Study Type	Number of Patients Patient Characteristics Methodology	Results on Quality of Life in EA survivors	Conclusion
Koivusalo et al (19) 2005	Case control study 1949-1979	159 EA survivors Control group 400 randomly chosen adults (200M 200F) **Response Rate of questionnaire** 128/159 (79.8%) EA patients 163/400 (41.5%) controls **Sex distribution** EA (57M and 71F) Control patients (63M 99F) **Median age** EA 38yrs (24-54) Controls 36yrs (20-56), p=NS **Educational Status** EA Academic grade 18% High school or vocational college 38% Skilled labourers 27% Basic Education 17% Controls Academic grade 12% High school or vocational college 29% Skilled labourers 40% Basic Education 19% **Grading of health** EA Excellent or good 71% Satisfactory 23% Poor 6% Control Excellent or good 80% Satisfactory 17% Poor 3% **EA Types** Type A 8 (6%) Type C 115 (91%) Type D 3 (2%) Type E 2 (1%) **Waterston classification** Group A 47% (60) Group B 34% (43) Group C 19% (25) **Types of EA Repair shown in Table 1** **Clinical data shown in Table 2**	**Incidence of Respiratory Symptoms** EA Moderate or Severe 9/128 (7%) Mild 32/128 (25%) Control Moderate or Severe 3/163 (1.8%) Mild 19/163 (11.7%) P<.05 **Respiratory Symptoms** EA SOB 14% Poor physical performance 33% Frequent coughing 7% Frequent respiratory infections 13% Copious mucus secretion 14% Controls SOB 9% Poor physical performance 20% Frequent coughing 3.6% Frequent respiratory infections 1.2% Copious mucus secretion 9% Mean RSRQLI scores were significantly higher in control subjects than in EA patients In both groups scores were high suggesting low overall incidence of significant respiratory symptoms **Significantly higher incidence of low (<45) RSRQLI levels in EA patients (Table 3)** **Incidence of Gastrointestinal Symptoms** EA Moderate or severe 12 (9.4%) Mild 38 (29.7%) Control Moderate or severe 10 (6.1%) Mild 43 (26.4%) P=NS Mean GIQLI scores were not significantly different between EA patients and controls or between different types of EA There was no difference in incidence of low scores (<105), Table 3 In subdivisions of GIQLI significant symptoms of GER occurred in 24/128 (19%) of EA subjects vs 14/163 (8.5%) of control subjects, p<.05 No difference in incidence of GI symptoms, GIQLI or GIQLI subsections between EA patients with different types of conduit	According to SF 36 and Visual Analog Scale the HRQol of EA patients was not worse than that of general population However significant respiratory or GER symptoms were seen in approximately 20% of EA patients which was significantly more than in control subjects Low scores of GIQLI and RSRQLI were common in EA patients with low HRQoL in generic SF 36 tests Interestingly psychiatric, musculoskeletal or acquired problems affected HRQoL of EA patients more often than associated respiratory and GI symptoms Low scores in GIQLI and RSRQLI were common (37%) in EA patients with low SF 36 generic tests In GIQLI no differences between EA patients and control subjects in total score Only the GIQLI dimension measuring GER was lower in EA patients QOL did not differ significantly between different EA Types or between different types of esophageal reconstruction. QOL in GIQLI and Visual analog scale was non-significantly lower in patients with colon interposition. But the functional and social problems in EA patients with gastric or colon interposition improved in the 20s No differences in any of the tests of psychosocial functioning (BDI, RSES, CTML) were found between EA patients and control subjects Complaints of thoracic scar and wing scapula were common in EA patients, indicating the need for improved surgical techniques

		Methodology **Questionnaires used** Health Disease and Education RAND 36 item Health Survey Form SF 36 only sent to EA patients Respiratory symptoms related quality of life index RSRQLI Gastrointestinal quality of life index GIQLI Tests of psychosocial functioning measured by Rosenberg Self Esteem Scale (RSES) and Beck Depression Index (BDI) and Cohen's Test for Life Management Ability	**GI symptoms** EA Difficulty swallowing 10% Slowness of eating 18% Regurgitation 17% Controls Difficulty swallowing 2% Slowness of eating 1% Regurgitation 10% P<.05 in all Incidence of musculoskeletal problems and acquired diseases did not differ between EA and control subjects EA Musculoskeletal disorders 19/128 (14.8%) Psychiatric disorders 6/128 (4.7%) Diabetes and Allergies 2/128 (1.5%) Hypertension 3/128 (2%) No acquired diseases 77 (60%) Control Musculoskeletal disorders 16/163 (9.8%) Psychiatric disorders 5/163 (3.1%) Diabetes and Allergies 4/163 (2.5%) Hypertension 6/163 (3.6%) No acquired diseases 116 (71%) Assessment of HRQol and SF36 showed poor quality of life in physical and mental domains in 19 (14.8%) of EA patients, which was within the expected incidence of 16% Results of SF36 did not differ between different EA Types QOL by Visual Analog Scale did not differ between EA and control subjects (Table 4) Health problems that EA patients graded as significant related to acquired diseases (n=11) Psychiatric problems 5 Musculoskeletal problems 3 HT 2 Malignancy 1 Or Congenital or EA related diseases 8 Hair cartilage dysplasia 1 Functional GI disorders 2 GER 2 Respiratory problems 1 Vaginal atresia/vulvodynia 1 Mental retardation 1 Of the 19 EA patients with low HRQol scores, 7 had low GIQLI scores and 4 had low RSRQLI scores, 3 had low scores in both	

			Mean scores in tests of psychosocial functioning EA BDI 31.8 (4.7) RSES 45.2 (7.4) CTML 53.9 (10.6) Control BDI 31.9 (4.1) RSES 45.9 (9) CTML 54.6 (8) P=NS between both groups **Incidence of low scores** EA BDI 13.3% RSES 15.6% CTML 7.8% Control BDI 8.6% RSES 9.2% CTML 6.1% P=NS between both groups **Scar complaints** EA 64 (50.3%) had no complaints 42 (34%) had minor complaints 20 (15.6%) had significant complaints 14 (11%) had "Wing" scapula	

Table 1 The type of esophageal repair

Type	Primary anastomosis	Colon interposition	Gastric tube	Closure of TEF	Skin tube	Total
C	109	6[a]				113
A	1	3	3[b]		1[c]	8
E	0	0		2		2
D	2	1[d]				3
Total	112	10	3	2	1	128

[a] Two patients with long gap type C and 4 with failed primary anastomosis.
[b] Three patients with failed colon interposition.
[c] One patient with failed colon interposition and gastric tube.
[d] One patient with failed primary anastomosis.

Table 2 Clinical data of 128 patients with EA

Median birth weight (g)		2910 (1520-4280)
Birth weight <2500 grams		25
Median length of primary hospitalization (d)		46 (9-335)
Median length of secondary hospitalization (d)		31 (21-121) (n = 32)
Associated anomalies (n)	Cardiac	4
	Chromosomal	2
	Anorectal	6
	Other GI	2
	Genitourinary	7
	Extremities	6
	Vertebra	4
	Cheilopalatoschisis	5
	Omphalocele	1
	Hair-cartilage hypoplasia	1
Major complications (n)	Leakage in primary anastomosis	8
	Leakage/cervical fistula after colon interposition	2
	Recurrent TEF	4
	Stricture of primary anastomosis requiring resection and reanastomosis	2
Tracheomalacia requiring aortopexy (no. of patients)		8
Fundoplication (no. of patients)		2
Dilatation/calibration of primary anastomosis [median (range)]		6 (1-56) sessions (n = 109)

Table 3 Respiratory symptoms–related quality of life index and GIQLI in 128 patients with EA and 163 control subjects and in different types of EA and in different types of esophageal repairs

	RSRQLI mean (SD)	*P*	Low RSRQLI	*P*	GIQLI mean (SD)	*P*	Low GIQLI	*P*
Control subjects (n = 163)	58.9 (4.3)	<.05	3	<.05	124.3 (13.8)	NS	13	NS
EA (n = 128)	55.3 (7.2)		10		121.9 (16.4)		17	
C (n = 115)	55.6 (7.2)	NS			122.5 (16.2)	NS		
A (n = 8)	51.4 (7.3)		114.6 (19.0)					
E (n = 2)	54.0 (7.1)		127.0 (19.8)					
D (n = 3)	56.3 (9.1)		121.3 (19.6)					
Primary anastomosis (n = 112)	55.6 (7.3)	NS	122.7 (17.9)	NS				
Colon interposition (n = 10)	54.7 (6.0)		115.3 (17.9)					
Gastric tube (n = 3)	50.3 (9.2)		119.5 (17.7)					
Thoracic skin Tube (n =1)	53.0		123.0					

Low RSRQLI <45/60, Low GIQLI <105/144.

Table 4 Health-related quality of life (SF-36) and quality of life measured in Visual Analog Scale (QoLVAS)

	n	Low HRQoL mental health	Low HRQoL physical health	Low HRQoL mental and/or physical health	*P*	QoLVAS	*P*
Control subjects	163	–	–	–		82 (12)	NS
EA	128	11 (8.6%)	13 (10.1%)	19 (14.8%)	81 (12)		
Type C	115	10	12	18	NS	80 (13)	NS
Type A	8	1	1	1		79 (8)	
Type E	2	0	0	0		85 (5)	
Type D	3	0	0	0		82 (13)	
Primary anastomosis	112			16	NS	81 (12)	NS
Colon interposition	10			3		77 (14)	
Gastric tube	3			0		82 (5)	
Thoracic skin tube	1			0		80 (0)	