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Long-Gap Esophageal Atresia: a Meta-Analysis of Jejunal Interposition, Colon Interposition, and Gastric Pull-Up

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Abstract

Aim There is still no consensus about the optimal surgical approach for esophageal replacement in the case of long-gap esophageal atresia (LGEA) or extensive corrosive strictures. The aim of this article was to perform a meta-analysis comparing the most widely used techniques for esophageal replacement in children: jejunal interposition (JI), colon interposition (CI), and gastric pull-up (GPU).

Methods Review of the English-language literature published in the past 5 years about esophageal replacement in children was done. The focus was on postoperative survival rate, morbidity (gastrointestinal complications such as anastomotic stenosis/leakage and respiratory complications such as pneumothorax, pneumonia, and atelectasis), and long-term follow-up when available. Among long-term gastrointestinal outcomes were dysphagia, reflux, and dumping; among long-term respiratory outcomes were recurrent pneumonia and recurrent aspiration leading to chronic lung disease. Data were computed by Comprehensive Meta-Analysis software (Version 2.2.064).

Main Results A total of 15 studies (4 comparative retrospective, 8 retrospective, and 3 prospective) including 470 patients (264 LGEA) were identified; 344 (73%) patients underwent CI, 99 (21%) GPU, and 27 (6%) JI. Among these 15 studies, 9 provided data about long-term follow-up.

Conclusion Proper prospective comparative studies are lacking. GPU and CI appear comparable regarding postoperative mortality, anastomotic complications, and graft loss. On the long-term, GPU seems to be associated with a higher respiratory morbidity but fewer gastrointestinal complications than CI. Based on this article only two series provide data about JI, and they show highly divergent results. JI appears to be a valid replacement technique when performed by experienced centers; however larger numbers are needed to assess the outcomes of this procedure.

Keywords

- ▶ long-gap esophageal atresia
- ▶ esophageal replacement
- ▶ meta-analysis

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Introduction

There is still no consensus about the optimal surgical approach for esophageal replacement in the case of long-gap esophageal atresia (LGEA) or extensive corrosive strictures. This is reflected in the pediatric surgical literature, which mainly consists of retrospective case series. To provide an overview of the literature of the past 5 years, taking into account the methodological and numerical differences among the considered studies, we have performed a meta-analysis comparing the three most widely used techniques for esophageal replacement in children: jejunal interposition (JI), colon interposition (CI), and gastric pull-up (GPU).

Methods

Literature

A literature search (PubMed and Embase) was performed, and all human studies published in the English-language literature between 2006 and 2011 describing esophageal replacement for LGEA were identified, using the medical subject headings "Esophageal Atresia," "Long-gap," "Esophagoplasty," "Replacement," "Interposition," "Substitution," "Graft," and their combinations. All titles and abstracts were scanned and appropriate citations were reviewed. Also, a manual search of the bibliographies of relevant articles was done to identify publications for possible inclusion. Included were prospective, retrospective, and comparative studies. Case reports, earlier reports of the series that were republished by the same center, review articles summarizing results of previous series, and the publications that did not provide sufficient data for the analyses mentioned above were excluded.

Definition of Outcomes

The articles were reviewed with a special focus on mortality, postoperative morbidity, and long-term follow-up. Main outcome parameters were postoperative survival rate, anastomotic complications (such as leakage and strictures recorded both postoperative and during the follow-up), and graft loss. Secondary outcome parameters were early respiratory complications (pneumothorax, pneumonia, atelectasis, mediastinitis, pleural effusion, and temporary diaphragm/vocal cord paresis), hospital stay, and intensive care unit (ICU) stay. Long-term follow-up was focused on gastrointestinal and respiratory outcomes, when defined. Long-term gastrointestinal outcomes were dysphagia, reflux, dumping, esophagus ulceration, anastomotic diverticulum, cervical fistula, graft redundancy, graft ulceration, intestinal obstruction, short bowel syndrome, dumping syndrome, delayed gastric emptying, cyclical vomiting, pyloric stenosis, diarrhea, colitis, peritonitis, small intestinal ischemia, and stomach perforation. Long-term respiratory outcomes were recurrent pneumonia, recurrent aspiration leading to chronic lung disease, and chest infection. Complications were recorded as stated in the article under review. When possible the exact number of specific complications were identified, otherwise the article was not included in the analysis (for that specific outcome).

Statistical Analysis

Studies were divided into the following three groups: JI, CI, and GPU. To perform the statistical overview Comprehensive Meta Analysis software (Version 2.2.064) was used. Data were computed using a random effects approach. To ensure that all effect sizes are represented in the calculated estimate, we did not perform a fixed effects analysis as we wanted to avoid giving more or less weight to larger or smaller studies. Under the random effects model the goal is not to estimate one true effect, but rather to estimate the mean of a distribution of effects in a range of studies, thus avoiding the overall estimate to be overly influenced by any study. Therefore, to obtain the most precise estimate of the overall mean (to minimize the variance among studies, given by within-study variance and the between-studies variance) we computed a weighted mean, where the weight assigned to each study is the inverse of that study's variance. Furthermore when the event rate in a study was equal to 0, 0.5 was added to event and nonevent values for the computation of Logit event rate and its variance.¹

However, there are only two studies regarding JI and the reported results differ widely. Because of this large divergence in results, calculating only an overall weighted mean using a random effects model seems inappropriate. For this reason, we present both the raw data and the weighted mean as described previously. Relative risks (RRs) were computed using JI as the standard to which the other procedures were compared. This implies that the treatment benefit for CI and GPU when compared with JI was associated with an RR less than 1.

Results

Data Collection

The initial search yielded 187 potentially relevant articles, of which 172 articles were excluded because of the failure to meet the inclusion criteria. A total of 15 studies fulfilled the inclusion criteria and were analyzed in this review (→ Table 1).^{2–16} Data about postoperative mortality and morbidity were given in 14 studies with a total of 470 patients (264 LGEA); 344 (73%) patients underwent CI, 99 (21%) children underwent GPU, and 27 (6%) patients underwent JI.

Among these studies nine reported follow-up data. One of these studies focused exclusively on follow-up after the treatment of corrosive esophageal strictures. This study was also included in the present article (107 patients treated by GPU and 69 by CI), so that long-term gastrointestinal data were available for 394 children: 207 (52%) after CI, 27 (7%) after JI, 160 (41%) after GPU. Respiratory data were available for 377 children: 190 after CI (50%), 27 after JI (7%), and 160 after GPU (43%). The majority of long-term data regards patients treated for corrosive strictures, followed by those treated for LGEA. The follow-up period ranged from 0.5 to 41 years.

Main Outcome Measures

Mortality is similar: postoperative survival rate after CI was 96%, after GPU 90.4%.

Anastomotic strictures (16.3% after CI vs 17.7% after GPU) and graft loss (4.2% after CI vs 4.8% after GPU) are comparable after these two procedures. Anastomotic leaks are reported

Table 1 Articles included in the present study

Author (year)	Replacement performed	Patients suitable for the present analysis	Study type
Tannuri et al (2007)	CI/GPU	115	Comparative Retrospective
Hunter et al (2009)	CI/GPU	11	Comparative Retrospective
Holland et al (2009)	CI/GPU	25	Comparative Retrospective
Javed et al (2011)	CI/GPU	176	Comparative Retrospective
Burgos et al (2009)	CI	96	Retrospective
Hamza (2009)	CI	97	Retrospective
Esteves et al (2010)	CI	5	Retrospective
Coopman et al (2008)	CI	17	Retrospective
Bax (2007)	JI	19	Retrospective
Cauchi et al (2007)	JI	8	Retrospective
Stanwell et al (2010)	GPU	5	Retrospective
Tannuri et al (2008)	GPU	35	Retrospective
Gupta et al (2007)	GPU	27	Prospective
Esteves et al (2009)	GPU	4	Prospective
Sharma et al (2011)	GPU	6	Prospective

Abbreviations: CI, colon interposition; GPU, gastric pull-up; JI, jejunal interposition.

more frequently after GPU (24.1 vs 17.3% after CI). Regarding JI, neither Bax nor Cauchi et al describe postoperative deaths. Both mention the occurrence of anastomotic strictures in 50% of the patients. Cauchi et al's series stands out by the high incidence of graft loss (37% vs no graft loss in Bax's series) and a higher incidence of anastomotic leakage (50 vs 26% in Bax's series). Reoperations (because of graft loss, evisceration, and redo anastomosis because of anastomotic leaks) were necessary in 15% of patients (4/27) after JI (4/8 in Cauchi et al's series vs 0/19 in Bax's series), in 6% (21/344) after CI, and in 3% (3/99) after GPU. Early respiratory morbidity has the highest incidence after GPU (24.6%); however all the three procedures seem to be comparable for this outcome (JI 22.3%, CI 20.8%). Hospital stay and ICU stay could not be computed from the articles. ▶ **Table 2a** depicts the main outcome parameters, graft loss, and early respiratory morbidity.

Long-Term Gastrointestinal and Respiratory Outcomes

▶ **Tables 2b** and **2c** depict the long-term respiratory complications and gastrointestinal complications after the three different reconstructions. When compared with GPU, CI has more reported gastrointestinal complaints (40.3 vs 35.4%) but slightly less respiratory problems (7.0 vs 10.8%). In the JI group, the incidence of late respiratory morbidity was 38% in the Cauchi et al's series as compared with 5% in the Bax's series.

Discussion

The present article set out to perform a meta-analysis of the literature regarding esophageal replacement for LGEA or

extensive corrosive strictures. There are few prospective series, amounting to only 37 patients. Well-designed prospective comparative studies are lacking, major and minor postoperative complications are sometimes not properly defined, follow-up data are often deficient and when presented they are not homogeneously described in the different studies. These make comparison a challenging task. Moreover, CI makes up for the majority of the surgical procedures reported. Far fewer studies describe the results of GPU and only two authors have illustrated their experience with JI.

If all studies about esophageal replacement for LGEA were similar we could compute a simple mean of the effect sizes, but considering the above mentioned methodological heterogeneity a simple comparison of the mean of the event rates described by different investigators seems inadequate. For this reason, we used a random effects model, using a weighted analysis of the most recent studies. Therefore the data depict an estimated overall effect. One should realize that this is only an approximation of reality and that conclusions should be carefully considered. However there are some tendencies that undeniably draw attention.

Importantly, there is little mortality regardless of the type of replacement. In contrast, morbidity is significant. In 470 patients, 93 early respiratory complications and 262 early gastrointestinal complications are reported. Reoperations (e.g., because of graft loss or anastomotic leaks) were necessary in 6% of patients. Reoperation was most prevalent in one of the two JI studies, mainly because of dismal results in this small series (Cauchi et al's). However, the reoperation rate of 6% probably is an underestimation, as anastomotic strictures

Table 2a Main outcome parameters by type of surgery, graft loss, and early respiratory system complications

	Jejunum interposition				Colon interposition		Gastric pull-up	
	Weighted event rate	Events/ Total	Bax	Cauchi et al	Weighted event rate	Events/ total	Weighted event rate	Events/ total
Postoperative survival rate (%)	96.3 (77.8–99.5)	27/27	19/19	8/8	96.2 (93.3–97.9)	335/344	90.4 (82.3–95.1)	93/99
RR (95% CI)	1				0.97 (0.95–0.99)		0.93 (0.89–0.98)	
Anastomotic leakage (%)	33.9 (18.4–53.9)	9/27	5/19	4/8	17.3 (10.0–28.3)	67/344	24.1 (14.7–36.9)	21/99
RR (95% CI)	1				0.58 (0.32–1.03)		0.63 (0.33–1.22)	
Anastomotic stenosis (%)	51.9 (33.6–69.6)	14/27	10/19	4/8	16.3 (8.6–28.9)	44/344	17.7 (8.6–33.1)	16/99
RR (95% CI)	1				0.24 (0.15–0.38)		0.31 (0.17–0.55)	
Graft loss %	13.6 (0.7–77.0)	3/27	0/19	3/8	4.2 (1.5–11.0)	7/344	4.8 (1.8–12.2)	1/99
RR (95% CI)	1				0.18 (0.05–0.66)		0.09 (0.00–0.83)	
Early RS complications (%)	22.3 (10.4–41.5)	6/27	4/19	2/8	20.8 (14.8–28.3)	66/344	24.6 (12.3–3.2)	21/99
RR (95% CI)	1				0.86 (0.41–1.80)		0.95 (0.42–2.12)	

Abbreviations: CI, confidence interval; RR, relative risk.

were mentioned in 74 patients (16% of cases) and one might expect that many of these were dilated, which should be considered a reoperation. Unfortunately, only a few studies reported the number of required dilatations after anastomotic strictures, so this could not be computed in the present analysis. Although a conservative treatment of anastomotic leaks was described in the majority of the studies, redo anastomosis may have been underestimated as well in our results because a total amount of 97 anastomotic leaks was recorded. Still, in only five cases the authors clearly described a surgical revision of the leaking anastomosis. Only two series

describe the outcomes after JI. Bax et al report excellent results in their relatively large series (19 patients): no graft loss, anastomotic leaks in 26% of patients, strictures in 52%, and only a few respiratory problems after a median follow-up of 5.5 years. On the contrary, Cauchi et al described a small series (eight patients) where both anastomotic strictures and stenosis were present in 50% of patients. Graft loss, a devastating complication, was reported in 38%. Furthermore in Cauchi et al's series, after a comparable follow-up of 6.4 years, chronic pulmonary disease following recurrent aspiration and chest infections occurred respectively in three and two

Table 2b Long-term respiratory system complications by type of surgery

	Jejunum interposition				Colon interposition		Gastric pull-up	
	Weighted event rate	Events/ total	Bax	Cauchi et al	Weighted event rate	Events/ total	Weighted event rate	Events/ total
Overall late RS complications (%)	24.7 (1.2–90.2)	6/27	1/19	5/8	7.0 (1.7–24.0)	14/190	10.8 (4.9–22.2)	17/160
RR (95% CI)	1				0.33 (0.13–0.78)		0.47 (1.10–0.20)	
Recurrent pneumonia (%)	3.7 (0.5–22.2)	0 /27	0/0	0/0	2.9 (0.6–12.2)	1/190	2.6 (0.4–16.6)	2 /160
Chronic pulmonary disease following recurrent aspiration (%)	13.6 (0.7–77.0)	3 /27	0/19	3/8	5.5 (1.2–21.4)	13/190	5.9 (1.2–25.0)	15/160
Chest infection	10.8 (1.0–58.6)	2/27	0/19	2/8	2.0 (0.6–6.8)	0/190	1.2 (0.2–5.6)	0/160
Others	5.4 (1.1–22.7)	1/27	1/19	0/8	2.0 (0.6–6.8)	0/190	1.2 (0.2–5.6)	0/160

Abbreviations: CI, confidence interval; RR, relative risk; RS, respiratory system.

Table 2c Long-term gastrointestinal complications by type of surgery

	Jejunum interposition				Colon interposition		Gastric pull-up	
	Weighted event rate	Events/total	Bax	Cauchi et al	Weighted event rate	Events/total	Weighted event rate	Events/total
Overall late GIS complications (%)	24.0 (9.2–49.6)	6/27	3/19	3/8	40.3 (15.8–70.8)	81/207	35.4 (22.6–50.7)	54/160
RR (95% CI)	1				2.41 (1.13–5.11)		2.08 (0.96–0.46)	
Reflux	11.1 (3.6–29.4)	3/27	2/19	1/8	5.3 (0.7–30.0)	23/207	2.9 (0.3–25.1)	3/160
Dysphagia	3.7 (0.5–22.2)	0/27	0/19	0/8	7.2 (2.2–1.0.3)	16/207	7.9 (1.8–28.5)	20/160
Other	13.2 (2.6–46.4)	3/27	1/19	2/8	24.4 (8.8–51.9)	42/207	22.3 (13.0–35.5)	31/160

Abbreviations: CI, confidence interval; RR, relative risk; GIS, gastrointestinal system.

out of eight patients. These deeply divergent findings might be related to technical issues but also the small number of patients included in the series of Cauchi et al might have influenced the results. What both studies share are the absence of postoperative death and a considerable high incidence of anastomotic complications (→Table 2a). The main reason for this is the fact that the distal esophagus is usually small and hypoplastic. End-to-end anastomosis tended to lead to a functional stenosis. Since changing the technique to a more oblique anastomosis at the distal esophagus the complication was seen less frequently. The low incidence of dysphagia might be because of the fact that jejunum retains peristaltic activity and thereby functions as an active conduit. However, this should also diminish the occurrence and severity of reflux. The data from the present

meta-analysis suggest that GPU and CI are comparable regarding postoperative survival rate, anastomotic strictures, and graft loss. Anastomotic leakage might be more present after GPU. The tension sustained by the single anastomosis performed during GPU might add to this, although the incidence of anastomotic stenosis is equal to CI. Respiratory morbidity (both postoperative and long term) appears to be more prevalent after GPU. This might be related to the loss of the “Angle of His” following the mobilization of the stomach in the mediastinum. This may contribute to reflux and, as a result, to (micro) aspiration, especially when considering the negative intrathoracic pressure. Maybe most important, the bulk of the stomach is situated in the chest, which may impair respiration.¹⁷ Long-term gastrointestinal morbidity seems to be more prevalent after CI. The gastrointestinal function after

Table 3 Possible standardized outcomes

Preoperative outcomes	Intra- and postoperative outcomes	Follow-up
Gestational age	Type of surgery (open/laparothoroscopic)	Length of follow-up
Birth weight	Age at surgery	Growth curves at last control
Type atresia	ICU stay/intubation length	Oral/tube feeding
Gap length	Standardized morbidity rate	Standardized morbidity rate
Cervical esophagostomy	<ul style="list-style-type: none"> – gastrointestinal: <ul style="list-style-type: none"> anastomotic stenosis anastomotic leaks anastomotic reinterventions graft loss – respiratory: <ul style="list-style-type: none"> pneumothorax pneumonia mediastinitis pleural effusion 	<ul style="list-style-type: none"> – gastrointestinal <ul style="list-style-type: none"> reflux dysphagia anastomotic reinterventions – respiratory <ul style="list-style-type: none"> aspiration recurrent pneumonia asthma like symptoms
	Mortality	Mortality

Abbreviation: ICU, intensive care unit.

this approach might be affected by the usual absence of peristalsis in the colon, so that the transit is given only by gravity. Moreover graft redundancy was also recorded significantly more often after CI and, when leading to food retention, it could contribute to regurgitation and potentially to aspiration. A combination of these conditions might explain the higher event rate of reflux after CI when compared with that after GPU. Concluding, from this systematic review of the most recent experiences in esophageal replacement for LGEA and extensive corrosive strictures, no surgical approach emerges distinctly as the best procedure. Comparison is challenging as outcomes are reported differently. GPU and CI appear comparable regarding the main outcomes of the present study: postoperative mortality, anastomotic complications, and graft loss. GPU seems to be associated with a higher respiratory morbidity but fewer gastrointestinal complications than CI. Based on the present article only two series provide data about JI, and they show highly divergent results. JI appears to be a valid replacement technique when performed by experienced centers; however larger numbers are needed to assess the outcomes of this procedure. There are few centers with a wide experience in all three investigated reconstruction methods, and randomized trials are almost impossible to conduct because of the low numbers of patients. Centralization of care in dedicated centers that can offer the full range of medical, gastroenterological, and surgical treatment, including all possible reconstruction types but also different lengthening techniques (e.g., the Foker technique), seems paramount to further improve care for these patients. In the future, large series from these centers may offer a better insight in the results of care for this difficult patients group. In the present article the review process was complicated by the fact that the data were not homogeneously described in the selected publications. To avoid this heterogeneity in the future, it might be feasible for authors to describe a structure of common outcomes to share the same setting among different reports, such as the use of standardized definitions of complications and long-term outcomes (→ Table 3).

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Conflict of Interest

None

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