Long-gap esophageal atresia treated by growth induction: the biological potential and early follow-up results

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This study had two purposes. The first was to determine whether the growth procedure would allow true primary repairs of the most severe end of the esophageal atresia (EA) spectrum with the longest gaps (LG) and most rudimentary lower esophageal segments. The second goal was to provide the first short-to mid-term (3-12 years) follow-up data on the esophageal function and quality of life (QOL) data on the patients in this series. From our series of 60 LG-EA patients who underwent a growth procedure, 42 had the true primary esophageal repair completed 3 years ago. Among these, 18 had gaps over 6 cm, and for 6, only a rudimentary lower esophagus existed well below the diaphragm. No patient was turned down and all had primary repairs. These results suggest that even the most rudimentary segment has the potential to achieve normal size and that the full EA spectrum can have a primary repair. Our follow-up studies indicated that the esophageal function of these previously grown segments was very good. All contacted (40) were eating normally with only 3 receiving supplemental g-tube feeds because of other significant defects. We have actively treated significant reflux and 41/42 had fundoplication. By endoscopy (N = 15) no esophagitis was visible, but on biopsy, mild inflammation was found in 3. No conditions were found which would suggest that there would be a late deterioration or adverse consequences would arise. Based on these ongoing evaluations, the outlook seems very favorable for a good long-term QOL.

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KEYWORDS
Long gap; Esophageal atresia; Growth procedure; Mid-term function

Infants born with long-gap esophageal atresia (LG-EA) have posed a difficult treatment problem for pediatric surgeons.1,2 The many different repairs that have been used are a testimony to the problems encountered in obtaining a satisfactory result. The methods to establish continuity have ranged from time, myotomies and lengthening flaps to close shorter distances to the creation of gastric tubes, or the pulling up of stomach, small, or large bowel to span the longest gaps.3-11 All of these methods have some initial limitations and early complications, but even more important would seem to be the potential detrimental long-term consequences that may arise.12-14

It is the particular problem of pediatric surgeons that the goal should be for 70 or more good years and this is a stringent requirement. A primary repair using one’s own esophagus is considered best suited to reach this goal, and it has a consensus as the preferable choice. For the shorter gaps, as occurs with the more common lower tracheo-esophageal fistula, a primary repair is routinely achieved. It
ageal segment (Figure 1). Consequently, this was a hetero-
testinal anastomosis, previous operations, or small size of lower esoph-
the growth procedure because of gap length, presence of
some successes but are slow and unreliable. These methods, moreover, are only suitable for relatively favorable EA
defects with reasonable length of the upper and lower ends. The waiting approach may also require prolonged hospital-
izations and pulmonary complications with potentially ad-
verse developmental consequences may occur. Moreover,
when the lower esophageal segment does not reach the
diaphragm, a primary repair has not been considered pos-
sible. To meet this challenge, the growth procedure has
been designed to relatively rapidly close the longest gaps
and achieve a primary repair throughout the EA spectrum.
We have previously reported very early results with growth
induction and described the flexible surgical technique be-
hind it. This approach has been confirmed by a number
of surgeons. The purpose of this report was to assess how well the
growth procedure has achieved these goals to date. Specif-
ically, we will: (1) determine the value of the growth pro-
cedure in the treatment of the full spectrum of LG-EA, (2)
present additional early results of growth induction in
LG-EA patients, and, importantly, (3) present the first mid-
term results on the suitability of growth induction to provide
a functioning esophagus. Our overall goal was to determine
whether these patients, born with the most difficult EA
lesions, are achieving an essentially normal quality of life
and are without structural consequences that will likely be
detrimental later in life.

Materials and methods

From 1995 to 2007, 60 patients underwent a growth proce-
dure for LG-EA. Of these patients, 42 were at least 3 years
post primary repair, and provide an opportunity for a short-
to medium-term follow-up evaluation. The 42 (31 male, 11
female) patients had gaps of 3.3–12.5 cm (average 5.7 cm
and 15 with lengths of 6.0 cm or more). The distributions
were 28 Type A (pure esophageal atresia), 10 Type B
(proximal fistula to trachea), and 4 Type C (with a distal
tracheal fistula). Eighteen had undergone previous oper-
tions, which included takedown of a tracheoesophageal fis-
tula (n = 5), creation of a cervical (spit) fistula (n = 13, 8
right, 5 left), and/or an unsuccessful prior attempt at a
primary repair (n = 7). No patients were turned down for
the growth procedure because of gap length, presence of
fistulas, previous operations, or small size of lower esopha-
geal segment (Figure 1). Consequently, this was a hetero-
genous group from the standpoint of the type of esophageal
atresia, age, and previous operations.

The patients ranged from 4 days to 2.5 years old at the
time of the first esophageal operation at our institutions. The
growth procedure has been described, and through a 3-cm
right posterolateral thoracotomy incision, both segments
were located within the pleural space. When the lower
segment was below the diaphragm, in some cases it could be
retrieved through the hiatus by gentle traction on the tissues
accompanying the vagus nerve. In other cases, an abdom-
nal incision was required to locate the tiny lower seg-
ment diaphragm. Pledgeded traction sutures were placed
in the upper and lower esophageal segments, and for
external traction, these were brought out above and be-
low the incision. In some cases, internal tension was
applied to one or both segments by anchoring the traction
sutures in the prevertebral fascia.

The tension on the external sutures was increased one to
three times each day. Within these intervals, growth oc-
curred and the tension on the segments lessened, requiring
it to be retightened. The growth was followed by the loca-
tion of clips placed on the esophageal ends by daily chest
x-rays. When the growth was sufficient, the incision was
simply reopened and a true primary repair performed. Anas-
tomotic tension in the repair was often unavoidable; how-
ever, the anastomosis has been found to withstand this
tension.

For the patients 3 or more years from the primary esopha-
geal repair, follow-up was conducted by three methods
(average time of follow-up was 6.9 ± 2.8 years). The first
contact was by telephone or email to verify current infor-
mation and allow superficial questioning. The second was
by a mailed questionnaire, which determined the patient’s
progress in learning to eat, recorded problems after dis-
charge, subsequent hospitalizations, or procedures per-
formed (e.g., dilations, stricture resections or, redo fundop-
lications) and the current medications. Lastly, clinical
evaluations were done including a combination of esopha-
goscopy with biopsies, esophageal ultrasound, and manom-
ometry in patients returning either to the University of Minne-
sota or their home hospital. The results of these evaluations
were compiled and the findings assessed.

Informed consent was obtained and the study had IRB
approval (HSC 0502S67466).

Results

From 1995 to 2007, 60 patients underwent growth induction
for LG-EA. A relatively rapid growth response occurred in
all patients, allowing for a primary repair after a median of
14 ± 12.9 days on traction. The gastroesophageal (GE)
junction was kept below the diaphragm where it belongs
and the esophageal wall left intact (no myotomies). Forty-
two patients were at least 3 years out from the primary
repair and suitable for the follow-up evaluations. There
were 3 patients not included who had late deaths unrelated to the repair. One child died from recurrent pulmonary vein stenoses and complications of pulmonary hypertension, another from a primitive neuroectodermal tumor (PNET), and the third died 2 years after EA repair from complications of a small bowel volvulus treated at his home hospital.

The growth procedure has proven to be very flexible in solving the varying gaps and patient conditions we encountered. In general, external traction was required to produce adequate growth in the longest gaps, but in the cases of older children or complications of their previous operations, other combinations were used. Forty-two were at least 3 years from the primary esophageal repair and form the basis of this short-to mid-term follow-up study. For two, the families have not been located within the last 2 years which gave a potential follow-up pool of 40 patients.

The type of tension-induced growth was tailored to the individual patient’s situation. For the 42 patients, 29 had external traction only, 9 had a combination of external and internal traction, and 4 had only internal traction to close the LG-EA. Twenty had prior operations, and closure of a right spit fistula (N = 8) or a left spit fistula (N = 5) was required before growth induction. If the spit fistula was closed for the purpose of permitting external traction, it was allowed to heal for about 4 weeks. In 4 cases, the children were too old to adapt well to the creation of a blind upper pouch, and therefore, it was lengthened by advancing down the anterior chest wall (Kimura procedure). Although each lengthening would gain about 2 to 3 cm, in general, this procedure became less satisfactory when the level of the clavicle was reached and the upper esophagus was stretched over it. Drainage became more of a problem and advancements less effective.

Once the traction stage was reached, the ability to rapidly induce growth was surprisingly good and closed gaps of up to 12.5 cm. More recently, an older child who had eight previous operations, and left with a gap of 16.5 cm, had sufficient growth induced to have a true primary repair. The induced growth was sufficient to close all gaps, whatever the length, and it stimulated the smallest lower segments. It has been stated that a primary repair is not possible if the lower segment does not reach the diaphragm. In two cases,

Figure 1  This patient typifies the severe end of the LG-EA spectrum. Only a very rudimentary lower esophageal segment was present by contrast study (A) or endoscopy through the gastrostomy tube site (not shown). It was located well below the diaphragm. After the growth procedure using external traction, a normal sized lower esophagus resulted, which allowed a true primary repair with a typical anastomotic site (arrow) location (B). (This patient also had a cardiac repair.)
Our follow-up evaluation, which we consider to be very important, is ongoing. We have employed 3 types of low-up studies. Of the 42 survivors who are at least 3 years beyond primary repair after the growth procedure, we have had relatively recent contact whether by telephone or by email with 40 families. The other 2 patients are from itinerant families and so far cannot be located. Both patients, however, have been seen by their pediatricians at least 1 year after their discharge from here, and both were judged to be doing well. Although their current situation is not accurately known, they appear to have had a satisfactory result. This level of evaluation provided little objective detail; however, it did provide a measure of assurance that there were no later failures and function was generally satisfactory.

The two more detailed follow-up evaluation techniques have been by a mailed questionnaire and the more desirable complete clinical evaluation. The returned questionnaires indicated that 27/28 eat normally for age. In this group, only 2 gastrostomy tubes remained; one in a patient with severe problems from the CHARGE syndrome, and the other with severe problems from the VACTERL association. Their esophageal function was satisfactory, although their other lesions made supplemental feedings necessary.

An issue associated with colon and gastric interpositions is the presence of intermittent aspiration and repeated or even chronic pulmonary problems. None of the 28 LG-EA patients had symptoms suggesting aspiration. Furthermore, none required periodic anastomotic dilations (Table 1).

We have believed that GE reflux is the most significant remaining problem for EA patients, and when significant, have recommended a fundoplication as the best strategy. For the LG-EA group, 28/28 had a fundoplication, which is in distinct contrast to the 20% to 30% rate in the more routine EA/TEF patients. The fundoplications have been generally effective, and there are few symptoms suggestive of reflux. A relatively high percentage remain on antacid therapy; however, the indications were not clear.

The follow-up endoscopy appears to provide the most significant information (Table 2). None of the patients studied had visible esophagitis, although in 2/15 cases there were tongues or patches of gastric mucosa greater than 4 cm above the GE junction. The significance of these changes

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Questionnaire results (N = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeding Evaluation</td>
<td></td>
</tr>
<tr>
<td>Eat normally for age</td>
<td>27</td>
</tr>
<tr>
<td>G-tube supplements</td>
<td>2</td>
</tr>
<tr>
<td>Symptoms of aspiration</td>
<td>0</td>
</tr>
<tr>
<td>Continued dilations</td>
<td>0</td>
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<tr>
<td>Reflux Assessment</td>
<td></td>
</tr>
<tr>
<td>Fundoplication</td>
<td>28</td>
</tr>
<tr>
<td>No or possibly mild symptoms</td>
<td>28</td>
</tr>
<tr>
<td>On medications</td>
<td>16</td>
</tr>
<tr>
<td>Histological Findings</td>
<td></td>
</tr>
<tr>
<td>Upper esophagus</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Esophagitis</td>
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<tr>
<td></td>
<td>Eosinophils present</td>
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<td>Lower esophagus</td>
<td>Normal</td>
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<td>Mild carditis</td>
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However, no lower segment lumen was discernible initially by either contrast study or endoscopy through the g-tube site, and in four more, it was no more than 2 to 3 mm long (Figure 1).

For this series of patients, several postoperative complications were seen. During the period of tension, one or more of the traction sutures pulled out in seven patients. If one or two sutures pulled out, particularly toward the end of the growth period, nothing was done and the tension was supplied by the remaining sutures. In one case, all four sutures pulled out and the lower segment retracted. These sutures were replaced and, at the completion of growth, a very satisfactory primary anastomosis was performed.

For nine patients, the traction sutures had to be reconfigured. The need for reconfiguration of sutures took different forms. In general, when a very short lower segment was encountered initially, the traction sutures necessarily went more laterally to the chest wall. Later, to produce additional growth, the traction sutures had to be placed higher on the chest wall. For two patients, adhesions stopped growth and the segments had to be freed up. In another, the chest tube was not tethered away and eroded into the lower segment, necessitating a direct repair. None of these problems with the traction apparatus prevented sufficient growth for a true primary repair.

The endpoint was only the closing of the gap, which was always reached. Because of the considerable variation in gap length, patient size, and age, the amount of growth induced was quite variable. By making simple assumptions and calculations, the increase in esophageal mass ranged from a 20% increase for a large upper pouch to a 50-fold increase for the small lower esophageal segments. For the two infants, in whom no lower lumen was present initially and the lower segment was only 2 to 3 mm in length, the calculation of mass increase was not made because the number would have been unworkably large. The growth potential appears sufficient to close the longest gap even beginning with the smallest segment.

Following primary repair, a contrast study was done 2-3 weeks later to assess strictures and reflux. All had dilations begun with a goal of no visible narrowing. All 42 had fundoplications done and 12 had a redo fundoplication within 16 months.

Our follow-up evaluation, which we consider to be very important, is ongoing. We have employed 3 types of fol-
and how much is within the normal variation seen with autopsy studies are not clear. Nevertheless, we believe it needs to be followed and reassessed to determine whether it is a progressive condition.

The biopsy specimens showed mild esophagitis at the lower end of the esophagus in two cases although it was not apparent visually by endoscopy. Again, the significance is unclear, but we have recommended follow-up endoscopy in the future. We have attempted to take these children off antacid medication if no esophagitis is present. We believe that the percentage of those on medication is considerably larger than it needs to be, particularly when a well-functioning fundoplication is in place. Certainly long-term antacid therapy has several drawbacks, including cost and gastric mucosal changes, among others. The best result will be to have the children off of these medications and without evidence of significant or injurious reflux.

Discussion

We had two goals in this report. The first was to provide more information on the suitability of the growth procedure to solve the problem of ultra long gaps and very diminutive lower segments, even with previous operations, including left spit fistulas. We believe the answer to this question is clear. Even the most rudimentary lower esophageal segment has all the developmental information necessary to form what appears to be a normal lower half of the esophagus. Because the endpoint was the closure of the gap and suitability for a primary esophageal repair, the maximum potential for growth was not determined.

Our previous reports established the feasibility of growth induction as well as the flexibility of the procedure itself. For the longest gaps, external traction was used so the tension could be increased daily to make up for the decrease the force, is only one of many possible techniques to increase the uniformity of the follow-up evaluation. Some families believed the follow-up was so important that they assumed the entire cost; others felt, however, that the time and expense was too great, particularly if their child was doing very well. For these patients, we continue our efforts to have a complete evaluation at their home hospital. There is also great variation in the definition and treatment of these issues in the literature. The two main issues after a successful primary repair are GE reflux and anastomotic strictures. It was quickly apparent to us that neither of these important issues had a consistent method of grading or treatment. As a result, we developed our own approach which had as its basis the active pursuit of normalcy. By that, we meant our postrepair treatment would attempt to establish a normal diet, have the G-tube removed as soon as possible, not have them on long-term medications and they would enjoy normal activity.

The more objective data by questionnaire, esophagrams, and esophagoscopy and biopsy indicate good-to-excellent outcomes. The logical comparison group for our LG-EA patients would be those who have had the more common and routine EA/TEF repair. When compared with the literature reports on these groups, our patients are very similar. What comes through is the importance of GE reflux in determining the long-term outcomes. Because of variations in patient populations, therapeutic strategy, and methods of evaluation, the conclusion for the long-term significance of reflux varies widely. It is established that the amount of reflux increases with anastomotic tension and more difficult lesions such as LG-EA. Because the lower esophageal sphincter is a relatively subtle structure, it is not unexpected that the severe end of the spectrum will have a much greater incidence of reflux. It is also well known that below the anastomotic line in all postrepair EA patients, the esophageal contractions are uncoordinated and sporadic. Moreover, gastric motility may be depressed, further contributing to reflux. Certainly, when one considers a very diminutive lower esophageal segment, as shown in Figure 1A, it seems very likely that the LES will be deficient.

The second goal of this report was to present follow-up data on the patients who have undergone the growth procedure for LG-EA. Even though the follow-up on the first patient is only 12 years, nevertheless, the follow-up of 3.1 to 12.4 (average 6.4) years has already provided evidence that the growth procedure for LG-EA results in repair equivalent to the straightforward EA/TEF in terms of current quality of life. Very importantly, the evaluations also indicate that there are no long-term consequences or problems that these children will necessarily fall heir to in the future.

We acknowledge that the follow-up evaluations are incomplete. The current medical climate in the United States does not favor these evaluations and, if the patient is asymptomatic, the insurance companies typically do not authorize these studies. Furthermore, the patients are scattered all over the United States and parts of Europe, making the return to Minnesota expensive and time consuming. If the patients remained in their home area, there was great variation in what pediatric gastroenterologists and surgeons regard as optimum long-term treatment, follow-up intervals, and the types of examinations that should be performed. This variation was surprising and led us to recommend return to us to increase the uniformity of the follow-up evaluation. Some families believed the follow-up was so important that they assumed the entire cost; others felt, however, that the time and expense was too great, particularly if their child was doing very well. For these patients, we continue our efforts to have a complete evaluation at their home hospital.

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The two groups of questions this study addressed, first concerned the capabilities of the growth procedure and its possible limitations. The second group of questions assessed the longer term results with the growth procedure
and also with our overall postprimary repair approach to the LG-EA patients.

We now have a relatively large experience with the LG-EA spectrum, and no patient has been turned down either for gap length or number of previous operations. Our patient population came from throughout the U.S. and much of Europe, and was driven almost exclusively by the parents; therefore, no opportunity existed for a controlled series. Our first decade results indicate that these children are functioning as well as EA/TEF patients, and there seems to be relatively little potential for late problems which will almost certainly plague both the gastric and colonic interpositions.

Another question raised in the literature was whether or not the force of the traction would damage the segment itself. This clearly has not proven to be the case, and it is remarkable how normal these segments appear after growth. There is certainly no apparent evidence for injury, and supporting evidence comes from the follow-up studies.

The questions addressed by our follow-up studies reveal how well these relatively rapidly grown segments function. This follow-up evaluation also reflects our approach to the LG-EA patients after completion of the primary repair. We actively pursued normalcy by early evaluation (about 2 weeks postrepair) both of the anastomotic site and the competency of the GE junction. If the contrast study about 2 weeks postrepair indicated some degree of stricture, gentle dilations were begun at that time. The same study was used to evaluate reflux and, as has been previously reported, it is very common in the LG-EA group. It is well known that the consequences of significant reflux not only include esophagitis but also increase the strictureing tendency. As a consequence, all of the 42 patients had a Nissen fundoplication and gentle dilations were started within about 2 to 3 weeks of the primary repair. Subsequent dilations were typically performed at weekly or biweekly intervals with the goal being to open the anastomotic site to the size of the esophagus above and below. It is our opinion that frequent and relatively vigorous dilations cause the strictureing tendency to relent, and we have no children out over 3 years who are continuing to have dilations.

Our experience with patients from many states and other countries certainly revealed a wide range of opinions on what constitutes either a significant stricture or significant reflux. Our opinion has been that the treatment of reflux by a fundoplication will best reduce the strictureing tendency, minimize the reluctance to eat because of reflux, prevent esophagitis, and reduce or eliminate the consequences and expense of antacid medications. GE reflux is frequent in LG-EA where the existence not to mention the competence of the lower esophageal sphincter is uncertain, and recurrence after fundoplication is also a significant problem. For these reasons, we recommended fundoplication for significant reflux and for recurrence.

In summary, we believe that this study has demonstrated the efficacy of the growth procedure to treat the full spectrum of EA including those with most rudimentary lower segments and the longest gaps. This in turn indicates that even the smallest esophageal primordium is capable of a relatively rapid growth response into a normal sized segment of esophagus.

The second goal of this study was to provide mid-term follow-up data on these patients. Although there are limitations because not all patients have been thoroughly evaluated, those that have show an excellent functional result. Moreover, there is no evidence that those that have not returned for evaluation have had an unsatisfactory result. It is only those children with significant associated defects and syndromes who continue to have difficulties, although they are not related to esophageal function. By the standards of eating normally, the absence of significant symptoms, or the lack of need for continuing procedures such as esophageal dilation, these children appear to be doing very well. The LG-EA patients treated by the growth procedure and an early active course of dilations and treatment of GE reflux seem indistinguishable from the much more favorable short-gap EA/TEF patients. Very importantly, nothing we have uncovered suggests that this favorable situation will not persist over the decades to come. It does seem these children are on course to have a continuing good quality of life from an esophageal standpoint.

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