
Esophageal Atresia

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Abstract

Esophageal atresia is one of the most common life-threatening congenital malformations of the newborn baby. Today, survival rates are around 95% and mortality is related mainly to extreme prematurity or severe associated malformations, predominantly cardiac anomalies. Operative reconstruction of the continuity of the esophagus or replacement by other organs is the surgical option. A large variety of operative strategies have been elaborated and proposed in the past to achieve this goal. Most of the reports are retrospective and there is a definite need for multicenter prospective protocols to evaluate the methods and results. Long-term complications are strictures of the anastomotic region, esophageal, gastric reflux with esophagitis, and tracheomalacia. Despite these problems, the overall health-related quality in adult persons is good. However, long-term follow-up investigations into adulthood including esophageal endoscopy are indicated.

Keywords

Esophageal atresia • Associate malformations • Replacement • Anastomotic stricture •

Anastomotic fistula • Recurrence • Dysmotility • Gastric reflux • Tracheomalacia • Follow-up

Contents

Introduction	2
Incidence and Etiology	2
Embryology	3
Associated Malformations	3
Classification	4
Diagnosis	4
Prenatally	4
Symptoms Postnatal	5
Radiological Diagnosis	6
Management	6
Preoperative Management	6
Operative Management	7
Complications	13
Early Complications	13
Late Complications	14
Long-Term Follow-Up	15
Conclusions and Future Directions	17
Cross-References	17
References	17

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Introduction

The term congenital atresia of the esophagus describes a large group of variant malformations, which share a defect of the esophageal continuity with or without a fistula to the trachea or to the bronchi. It is one of the most life-threatening anomalies in a newborn baby, and quality of survival depends from early diagnosis and appropriate therapy. The first successful surgery of a 12 days old female baby was performed by Cameron Haight at the University of Michigan in 1941. Grown up to an adult lady, this patient gave birth to a newborn which suffered again from an esophageal atresia that was successfully operated in the same institution by Arnold Coran.

The history of surgical therapy of babies with esophageal atresia after Cameron Haight is a history of success starting with survival rates around 50% but reaching today nearly 100% when associated life-threatening malformations are excluded. The mainstays of this success are appropriate diagnosis, preoperative therapy, and reconstruction of the esophageal continuity with closure of an existing fistula or esophageal replacement if necessary.

Incidence and Etiology

The incidence of an esophageal atresia is 2.44 in 10,000 births (95% CI, 2.35–2.53), ranging between 1.77 and 3.68 according to a recent international surveillance program; among them are 68.6% with fistula and 25.5% without fistula (Nassar et al. 2012). The mean incidence from a Swedish national registry between 1987 and 2007 was 3.3 in 10,000 live births with little or no significant changes over time (Oddsberg et al. 2012). According to a French national registry, the prevalence in 2008 and 2009 was 1.97/10,000 live births. There is a 1.3 slightly higher incidence in males, which is not significant (Sfeir et al. 2013).

Most cases occur sporadically, and therefore, the etiology is likely to be multifactorial. A high number of associated anomalies points to a very early disturbance of the developing embryo

causing anomalies in multiple organ systems while disturbances in the later phase of the organogenesis may be responsible for rather isolated forms of esophageal atresia. A number of environmental risk factors such as infectious diseases or teratogens are discussed in the literature including exposure to thalidomide, statins, alcohol, smoking, contraceptive pills, hormones, as well as maternal diabetes or higher maternal age (Oddsberg et al. 2010; Felix et al. 2009). Recent studies show a 4.5 times higher risk after an assisted reproductive technology (Källén et al. 2010). There is ample evidence from human and animal studies that the anomaly can be genetically determined. A large number of different syndromes have been reported in association with esophageal atresia. The Feingold syndrome is caused by mutations of the *MYCN* gene and 30–40% of these patients have an esophageal atresia. Furthermore, gene deletions and mutations such as the *SOX2* (AEG syndrome), *MID1* (Opitz G syndrome), *GLI3* (Pallister–Hall syndrome), *CHD7* (CHARGE association – coloboma, heart disease, atresia choanae, retarded development, genital hypoplasia, and ear deformities with deafness), and X-linked Opitz syndrome are connected to a higher incidence of esophageal atresia (Felix et al. 2009). Chromosomal anomalies occur in 6–10% of all cases including Trisomy 13, 18, and 21, and the 22q11 deletion syndrome (Felix et al. 2009; Reutter and Ludwig 2013). Finally, the recurrence risk for a second child in parents with one affected child is around 0.5–2.0%, and the risk for a newborn born from an affected parent is around 3.0–4.0% (Solomon et al. 2012).

The so-called VATER association was first described by Quan and Smith (1973) as a non-random coincidence of Vertebral anomalies, Anal atresia, Esophageal atresia, Tracheo-esophageal fistula, and Renal malformation. The acronym was later expanded to VACTERL association in order to include Cardiac anomalies and Limb dysplasia. The prevalence is about one in 40,000 neonates. The involvement of genetic factors in the etiology of this association is supported by an increased prevalence in first-degree relatives and higher incidences in monozygotic twins, as well

as gene mutations, mitochondrial factors (Bartels et al. 2012; Brosens et al. 2013; Siebel and Solomon 2013). However, since most of the esophageal atresia cases occur sporadically there is most likely a heterogeneous and multifactorial pathogenesis involving different or multiple genes and signaling pathways.

Embryology

The normal foregut embryology is still controversial. Within the fourth week of human gestation, the separation of the esophagus and trachea takes place by folding of the primitive foregut. The theories include malformation of a lateral in-growing septum dividing the foregut from the airways. Deviation of the septum in one or the other direction results in esophageal atresia or tracheal atresia. The fistula is lined with respiratory epithelium leading to the hypothesis that it arises as a posterior branch of the trachea (Mc Laughlin et al. 2013). Tracheal cartilages and also esophageal muscle layers have been identified in the fistula wall (Mc Laughlin et al. 2013). The today existing major theories have been recently summarized (Merei and Hutson 2002).

Significant insights have been provided by the Adriamycin-induced rat/mouse model of esophageal atresia (Mc Laughlin et al. 2013). The model produces a range of malformations similar to the VACTERL association thereby providing new insights into the organogenesis and regulation of gene expression of tracheoesophageal anomalies. The dorsal–ventral of the signaling molecules and transcription factors prior to separation of the common foregut is important for the subsequent separation. There is strong evidence of a close relationship between an abnormal notochord and disturbed somatic segmentation resulting finally in vertebral anomalies, cardiac malformations, and foregut anomalies such as esophageal atresia (Hajduk et al. 2012; Jacobs et al. 2012; Felix et al. 2009). Further experiments have shown a major role of the Sonic hedgehog (Shh) signaling pathway, and it seems to be obvious that *Shh* gene and the signaling glycoprotein are involved in the

normal morphogenesis of organ systems such as notochord, vertebra, and differentiation of trachea and esophagus (Ioannides et al. 2003, 2010; Hajduk et al. 2011). Sox2 is another transcription factor playing an important role in the separation of the foregut. From these experiments, one must conclude that there is either a primary gene-related defect or any exogenous pathogenic insult must occur already within the first 10 days of pregnancy causing notochord dysfunction and leading secondarily to the manifestation of anomalies such as esophageal atresia (or anorectal atresia, renal malformations, and others).

Associated Malformations

Babies with an early-affected organogenesis and esophageal atresia suffer from a high number of associated malformations within a range of 40–80% (Sfeir et al. 2013; Oddsberg et al. 2010; Stoll et al. 2009; van Heurn et al. 2002). The most frequent associated anomalies are musculoskeletal malformations (20–70%), followed by cardiovascular (20–50%), genitourinary (15–25%), gastrointestinal (15–25%), and chromosomal anomalies (5–10%). The wide range of given percentages in the literature comes from differences in the diagnostic workup. A careful X-ray of the whole vertebral spine, counting the ribs and vertebra in the different segments, will show up to 70% associated skeletal malformations and/or numerical variations in patients with esophageal atresia. For a successful treatment strategy, it is important to take care about a detailed diagnostic workup which has a significant impact onto the outcome. The incidence of the VATER or VACTERL associations is around 20% in the esophageal atresia population, but two or more anomalies occur in nearly half of the patients.

Associated cardiovascular anomalies have a significant impact on the overall survival of infants with esophageal atresia, reducing the survival rate to 67% compared to 95% without cardiac anomaly (Leonard et al. 2001). The most common cardiac anomaly is the ventricular septal defect (19%), which is associated with an up to 16% mortality rate. Other common anomalies

Table 1 Anatomical classification

	Vogt-types	Gross-types	Percentage (%)
Absent esophagus	1	–	–
EA without fistula	2	A	8.5
EA with fistula:			
Proximal	3a	B	1.0
Distal	3b	C	85.0
Proximal and distal	3c	D	1.5
H-type fistula without atresia	4	E	4.0

include atrial septal defect (20%), tetralogy of Fallot (5%), coarctation (1%), or right descending aorta (4%). It is important to realize that only a few days after delivery some of these cardiac defects lead to a clinically evident heart insufficiency. Therefore, all patients with esophageal atresia should have an early echocardiography as well as ultrasound exams of the renal tract and the brain. The most common gastrointestinal-associated anomaly is anorectal atresia (9%) followed by duodenal atresia (5%), malrotation (4%), and other intestinal atresia (1%) (Stoll et al. 2009; Deurloo et al. 2002). Further associated malformations may involve nearly all organ systems leading to omphalocele, neural tube defects, diaphragmatic hernia, and other anomalies. As mentioned above, association with at least 18 different syndromes are described in up to 10% of patients including Holt–Oram syndrome, DiGeorge syndrome, Goldenhair syndrome, Trisomy 13, 18, 21, CHARGE syndrome (coloboma, heart defect, atresia choanae, retardation, genital hypoplasia, and ear deformities), and many others.

Classification

Classifications usually take their orientation on occurrence and type of tracheoesophageal fistula. The commonly used systems are those described by Vogt (1929) and Gross (1953). Vogt's extremely rare type 1, characterized by a more or less total lack of the esophagus is not included in Gross' classification. An isolated tracheoesophageal fistula (H-type fistula) is classified as type 4 or D, although it may belong to a different

spectrum because the esophagus is patent. In Gross' classification, congenital esophageal stenosis constitutes type E (Table 1 and Fig. 1). A complete list of all published variations of esophageal atresia is summarized in the dissertation work of Kluth (1976).

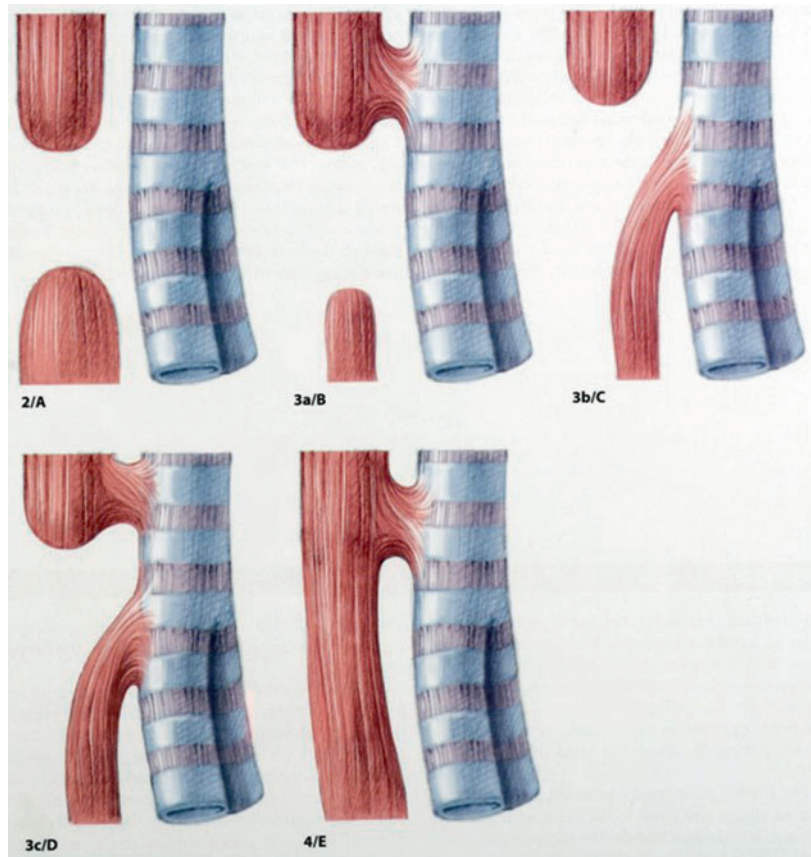
Additionally to the anatomical classification, there are risk classifications based on birth weight, cardiac anomalies, and/or pneumonia, which allow comparing the results of different institutions. The best known classification is named after Waterston et al. (1962). He suggested three groups based on birth weight, moderate associated anomalies, and severe, mostly cardiac malformations. A more recent classification adapted to the progress in neonatal surgery and medicine based on the experiences with 357 cases has been published by Spitz et al. (1994). In this classification, only birth weight and cardiac anomalies are the predicting factors for the prognosis (Table 2). Thus, still today associated cardiac malformations have a significant influence on the survival rate of patients.

Diagnosis

Prenatally

The earliest symptom of esophageal atresia is a polyhydramnion in the second half of pregnancy. Polyhydramnion is generally an unspecific manifestation either of swallowing disorders or of disturbed passage of fluid through the uppermost part of the intestinal tract of the fetus. Prenatal ultrasound may further reveal forward and backward shifting of fluid in the upper pouch and an absent

Fig. 1 The most common different forms of esophageal atresia (From Höllwarth ME in Puri P, Höllwarth ME, "Pediatric Surgery"; Springer Surgery Atlas Series, 2006)



stomach bubble. The positive predictive value of an absent stomach bubble and a polyhydramnion is 56%, and the sensitivity of prenatal ultrasound was found to be 42% (Stringer et al. 1995). In cases of a large tracheoesophageal fistula, the fluid swallowed by the fetus might pass through the trachea into the stomach, thereby preventing a polyhydramnion. Recently, fetal magnetic resonance imaging (MRI) has gained more attention for prenatal diagnosis of congenital anomalies.

Symptoms Postnatal

Postnatal presentation is characterized very soon by the typical drooling of saliva, choking, coughing, and cyanotic attacks. The abdomen rapidly distends due to the passage of air during inspiration through the fistula into the stomach. These symptoms are highly suggestive for

esophageal atresia, and therefore, any feeding trial is contraindicated because it causes early aspiration and pneumonia. The appropriate diagnostic step is to pass a 12 F (firm and X-ray visible) feeding tube into the stomach. If this is not successful, the diagnosis of an esophageal atresia is almost certain. However, small tubes must be avoided because they may curl up in the upper pouch thereby giving the illusion that they have been pushed forward into the stomach (Fig. 2). Very rarely, a small tube may pass through the trachea and through the fistula into the stomach, thus an esophageal atresia is erroneously excluded. If symptoms persist, a contrast radiograph should be performed demonstrating the atresia or even a small laryngotracheal cleft. If an esophageal atresia is suspected, a physical examination of the entire body must be performed in order to detect or exclude further associated malformations.

Table 2 Risk classification

	Waterstone	Survival (%)
Birthweight >2,500 g otherwise healthy	A	100
Birthweight 2,000–2,500 g or higher mild pneumonia or with moderate cardiac anomalies	B	85
Birthweight <2,000 g or higher, severe pneumonia, or severe associated cardiac anomalies	C	65
	Spitz	Survival (%)
Birthweight >1,500 g otherwise healthy	I	97
Birthweight <1,500 g or major cardiac anomaly	II	59
Birthweight <1,500 g, major cardiac anomaly	III	22

Radiological Diagnosis

The next step is to perform a plain X-ray including neck, thorax, and abdomen. The approximate length of the upper pouch can be estimated via the length of the X-ray visible tube in it. Air below the diaphragm can be seen in the presence of a lower tracheoesophageal fistula. Abdominal fluid levels are suspicious for an additional duodenal or intestinal atresia. A gasless abdomen indicates a pure esophageal atresia without a lower fistula (Fig. 3). A long distance between the segments is to be expected, but extremely rarely, a tiny or secondary occluded fistula may be present. The translucency of the lungs provides the first information whether aspiration occurred – either from saliva or from refluxed gastric acid through the lower fistula – is present. Some authors inject 0.5–1.0 ml water-soluble contrast material through the tube into the upper pouch under fluoroscopic control to detect a proximal tracheoesophageal fistula. Unrelated to the result, a preoperative tracheoscopy is always indicated to identify an upper fistula. Cardiologic assessment, including echocardiography, forms part of routine preoperative workup in order to recognize associated congenital cardiac anomalies or the presence of a right descending aorta, which might influence the surgical approach. Brain, abdominal, and urogenital ultrasounds are performed routinely. Finally, the skeletal X-ray should be analyzed carefully whether or not structural or numerical anomalies exist along the vertebral column or the ribs. Blood samples, as well as tissue samples, during surgery should be stored in a biobank for

genetic and chromosomal analysis even if the external aspect of the baby is not suspicious for a genetic defect.

The history of a patient with an H-type fistula without atresia is different: there is no passage problem, but leading symptoms are recurrent coughing and cyanotic attacks during feeding due to aspiration through the fistula. Presentation is usually more protracted and sometimes delayed beyond the first year of life. Diagnosis is made by esophagography with water soluble contrast material that shows the spillage of parts of the contrast material through the fistula into the trachea. Tracheoscopy confirms the diagnosis.

Management

Preoperative Management

The babies are nursed in the ICU. Immediate surgery is rarely required, so that all the above-mentioned investigations can be performed step by step. An oro- or nasoesophageal insertion of a double-lumen Replongle tube is mandatory for continuous or intermittent aspiration of saliva to prevent aspiration. The baby should be positioned upright to minimize gastroesophageal reflux through the fistula into the trachea and lungs via the fistula. Intubation and ventilation is only necessary in cases of respiratory distress, severe pneumonia, or severe associated malformations demanding respiratory therapy. In these cases, the endotracheal tube should be possibly positioned beyond a distal tracheoesophageal fistula



Fig. 2 In this case, a too small feeding tube was used to diagnose an esophageal atresia. It resulted in a curling up in the upper esophageal pouch misleading to the diagnosis of a normal esophagus. Therefore, a rather firm and thicker tube should be used for this procedure

to avoid insufflation of gas into the stomach with the risk of gastric perforation. If the latter problem cannot be avoided due to a very low opening of the fistula into the carina or the right main bronchus or due to a very large fistula, a gastrostomy with an underwater seal may ameliorate the problem. Gastrostomy and emergent surgical closure of the fistula by a thoracotomy is the best strategy to avoid severe respiratory distress and is also used in unstable or very premature babies. Broad spectrum antibiotics, intravenous fluid therapy, and vitamin K analogue are administered before surgery. If a severe pneumonia exists, surgery has to be postponed until the lung recovers. In the case of severe associated malformations (e.g., diaphragmatic hernia or cardiac malformation), it needs to be decided which surgical procedure comes first or whether they are performed in one step. Again, a preliminary closure of the fistula



Fig. 3 Esophageal atresia without lower esophageal fistula indicating a long distance between esophageal segments

saves time, but the anastomosis can be postponed if necessary.

Operative Management

Esophageal Atresia with Distal Tracheoesophageal Fistula (85%)

Surgical repair is performed under general anesthesia with endotracheal intubation. As mentioned above, the endotracheal tube is advanced close to the tracheal bifurcation and the infant is ventilated manually with rather low inspiratory pressure and small tidal volumes. It is advisable to start the procedure routinely with a *tracheobronchoscopy* using a rigid 3.5 mm endoscope. The trachea and main bronchi are briefly inspected, and the fistula to the esophagus is localized, which is usually 5–7 mm above the carina. Exceptionally, it may be found at the carina or even in the right main bronchus indicating a short lower segment and most likely a longer esophageal gap. The next step is to look for an upper fistula. The dorsal membranous region of the tracheal wall is

inspected carefully up to the cricoid's cartilage. Small upper fistulas can be missed. To avoid this pitfall, irregularities of the dorsal tracheal wall are gently probed with the tip of a 3 F ureteric catheter passed through the bronchoscope. If a fistula is present, the catheter will glide into it.

The goal of the surgical procedure is to divide the fistula, to close it on the tracheal side, and to perform an end-to-end anastomosis between the esophageal segments. Essential of the surgical part is a very careful and not tissue traumatizing procedure. The standard approach is through a right-sided laterodorsal thoracotomy via the fourth intercostal space. Muscle-sparing thoracotomy between the latissimus dorsi and the anterior serratus muscle reduces postoperative muscle function and pain (Mortell and Azizkhan 2009). Some authors use a high axillary skin crease incision for better cosmesis (Bianchi et al. 1998). A right-sided aortic arch is diagnosed preoperatively only in 20% and then a left-sided approach is recommended (Babu et al. 2000). If an unsuspected right-descending aorta is encountered, the procedure can be continued in most cases, establishing the anastomosis to the right of the aortic arch; however, the incidence of anastomotic fistulas seems to be higher (Babu et al. 2000). While in earlier times the procedure has always been performed extrapleurally, recent progress in surgical techniques and suture material as well as sophisticated perioperative management allows operating transpleurally without any disadvantage. The azygos vein is divided between ties and the fibres of the vagal nerve are preserved as good as possible. The fistula is closed near to the trachea but avoiding any narrowing of the airway. The anastomosis of the esophagus is performed with 6/0 absorbable sutures. To facilitate the identification of the upper pouch, the Replongle tube can be pushed forward by the anesthetist. After incision, the upper pouch mucosa often retracts and can be missed if the surgeon does not take particular care with the anastomosis. Once the posterior wall is sutured, a 5 F feeding tube is introduced into the stomach with one end and back to the mouth with the other end to allow early postoperative feeding. The routine use of an intercostal drain (ICD) is a

matter of debate today. A recent analysis of 96 consecutive patients without ICD did not show any disadvantage by omitting the drain (Paramalingam et al. 2013). Suture closure of the ribs supports the development of synostosis and possibly scoliosis but is not needed since alignment of the ribs occurs within a few days.

In the majority of the cases with a distal fistula, the goal of a tension-free anastomosis can be achieved. Occasionally, the distance between a short upper pouch and the lower esophageal segment is very long and anastomosis is only possible by mobilization of both segments. If the tension appears just a bit too much despite extensive mobilization of the lower esophagus and the upper pouch, further length may be gained with a circular myotomy (Livaditis et al. 1972; Lindahl 1987; Fig. 4). A serious complication that might occur is the ballooning of the mucosa and the development of a pseudodiverticulum (Otte et al. 1984). Another way to reduce inappropriate tension to the anastomosis is to fashion a mucosamuscular flap from a rather large upper esophageal pouch (Fig. 5). Collis gastroplasty or Schärli's division of the lesser curvature are rarely considered as useful options (Schärli 1992; Evans 1995). If there is no chance to achieve an acceptable anastomosis, the strategy should be for a delayed anastomosis after closing the fistula and performing a gastrostomy. Both segments are approximated by sutures as close as possible.

Some authors published successful thoracoscopic repair of the esophageal atresia, which is necessarily transpleural (Rothenberg

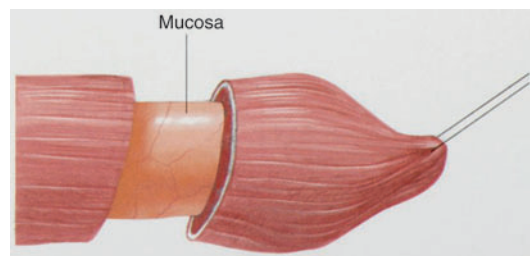
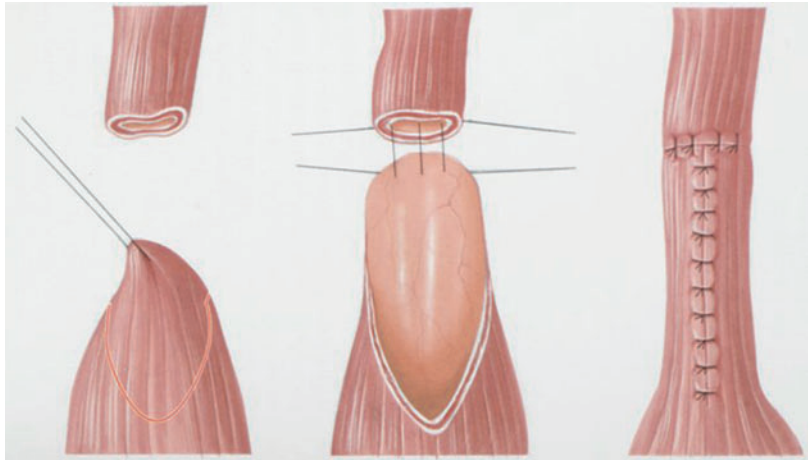


Fig. 4 The circular myotomy according to Livaditis can lengthen the upper esophageal pouch for 0.5–1.0 cm (From Höllwarth ME in Puri P, Höllwarth ME, “Pediatric Surgery”; Springer Surgery Atlas Series, 2006)

Fig. 5 If a very large upper esophageal pouch is present, a flap can be fashioned to bridge the distance to the lower esophagus (From Höllwarth ME in Puri P, Höllwarth ME, “Pediatric Surgery”; Springer Surgery Atlas Series, 2006)



and Flake 2015; Rothenberg 2013; Holocomb et al. 2005). Meta-analyses comparing open and endoscopic repair show similar complication rates regarding leaks and strictures but an earlier time to extubation and oral feeding as well as a shorter hospital stay after thoracoscopic approach (Yang et al. 2016; Borruto et al. 2012). However, the thoracoscopically performed anastomosis is certainly a very demanding procedure and needs great experience of the endoscopic surgeon. A carefully balanced discussion comparing the thoracoscopic repair with results of more recent carefully performed open surgical procedures concludes that the latter is still the “gold standard” for most of the surgeons, while thoracoscopy may be appropriate for very experienced teams (Laberge and Blair 2013). This opinion is confirmed by a recent international survey showing that 90% out of 178 contributing institutions perform an open, mostly extrapleural repair (71%) of the atresia, despite that endoscopic surgical procedures are performed routinely in most of these institutions (Zani et al. 2014).

Esophageal Atresia with Proximal and Distal Tracheoesophageal Fistula (1.5%)

As mentioned above a careful endoscopic examination of the dorsal tracheal wall using a 3 F ureteric catheter along the membrane enables the surgeon to detect an upper fistula which can be as high as the cricoid cartilage. The catheter can be

left in the fistula to facilitate the identification when the upper pouch is separated from the trachea. Any damage to the membranous trachea should be carefully avoided. The recurrent laryngeal nerve runs in the groove between trachea and esophagus and must be identified and protected. The fistula is divided flush to the trachea and closed on both sides with 6/0 sutures.

Esophageal Atresia with a Proximal Tracheoesophageal Fistula Only: A Long Gap Problem (1%)

In these cases, a long gap between the upper pouch and the lower esophagus has to be expected; therefore, a primary thoracotomy is not indicated. The first step is to perform a gastrostomy and to insert a radioopaque tube into the lower esophagus. The X-ray shows either a rather short lower esophageal pouch with a long distance between the segments or even a tiny anlage of esophagus which cannot be used for an anastomosis. The gastrostomy is needed for feeding the baby and, depending from the choice of the surgeon, for the longitudinal bougienage (see later in this chapter).

The upper fistula can be approached and identified via a right neck incision. A 3 F catheter that has been inserted during tracheoscopy allows an easy identification of the fistula, which is then divided and closed on both sides. The recurrent laryngeal nerve should be identified and preserved. The Replongle probe allows continuous

suction from the upper pouch until the final procedure will be performed.

H-Type Fistula (4%)

The fistula is identified by endoscopy and a 3 F ureteric catheter is passed across the fistula into the esophagus. Most H-type fistulas can be approached from the right side of the neck because they are usually situated at or above the level of the second thoracic vertebra. Palpation of the ureteric catheter facilitates the identification of the fistula. Again, the upper laryngeal nerve must be identified and carefully preserved.

The Long Gap Problem (8.5%)

An airless abdomen on thoracoabdominal X-ray leads to suspicions of an esophageal atresia without a lower fistula, and a long gap can be expected between the segments. The surgical management of this situation represents a major challenge which is extensively discussed in the literature.

The primary procedure consists of the placement of a gastrostomy tube to allow early enteral feeding. During this procedure, the distance between the pouches can be estimated by inserting a radio opaque tube in the upper pouch and in the lower pouch via the gastrostomy. A distance of three to four vertebral bodies on a chest film is considered as a "long gap," a distance of five vertebral bodies in the newborn is about 35 mm, and in the 6-month-old child 47 mm (Fig. 6a, b). However, there is no consensus about the definition of a long gap in the literature, and additionally, there exist many technical variations to measure the gap length, e.g., at birth or later or at the time of surgery, without pressure or with gentle or with strong pressure, pressure on one or on both segments, including a dynamometer to estimate forces, or with gas insufflation into the stomach (Table 3; Bagolan et al. 2013, Brown and Tam 1996). Thus, the terms long gap, very long gap, and ultra-long gap are used quite differently; therefore, cases and results from different institutions cannot easily be compared. The use of a retrograde esophagoscopy of the lower segment is useful not only to identify the length of the lower pouch but also to exclude the existence of

a so-called nipple-like distal esophageal remnant (Yeh et al. 2010).

Two basic surgical strategies are available in cases of a long gap esophageal atresia: either the preservation of the patient's own esophagus with delayed repair or esophageal replacement. There is consensus that all efforts should be directed to the salvage of the child's own esophagus because an ideal graft does not exist. Concerning the preservation of the native esophagus, three strategies exist: the first is to await spontaneous growth for 2–3 months; the second is to promote elongation within 3–6 weeks by bougienage of the lower and/or upper segment; and third is characterized by using internal or external traction forces in order to achieve an anastomosis within 8–12 days. In any case, it is essential to prove that a lower esophageal segment truly exists and is significantly different from a tiny nub at the upper end of the stomach. In the latter case, elongation procedures are useless and esophageal replacement should be planned primarily.

1. Delayed primary anastomosis

Basis of this strategy is to wait for spontaneous elongation of the esophageal segments that occurs at a faster rate than overall somatic growth due to the swallowing reflex and recurrent reflux of the gastric content. The maximal growth occurs within 8–12 weeks, and therefore, the ideal time for the delayed anastomosis was suggested at about 12 weeks. The distance between the segments is then usually <2.0 cm (Puri et al. 1992). A recent meta-analysis of 451 cases reported about a 50% leak rate, secondary resection of the anastomosis due to intensive stricture was necessary in 26/121 (21.5%), and esophageal replacement in 13/92 (14%) patients (Friedmacher and Puri 2012). The clear advantage of this strategy is that it needs only one thoracotomy, but a disadvantage of the method is the long waiting time, increasing the financial load and the risk of aspiration pneumonia. However, survival rates as well as long-term results are excellent when compared with other methods (Ein et al. 1993; Paran et al. 2007).

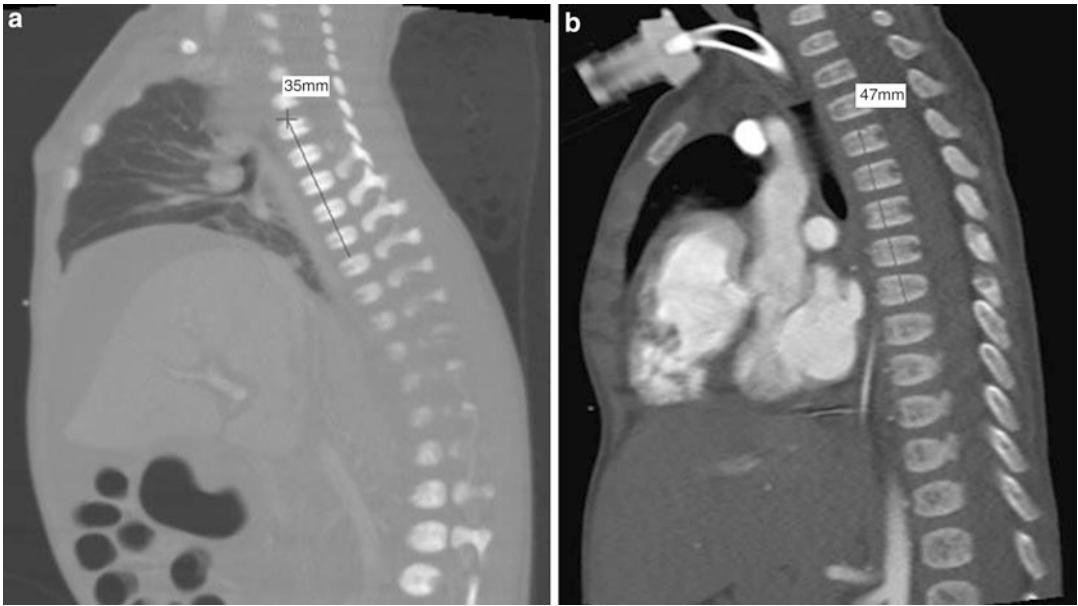


Fig. 6 (a) The length of five vertebral bodies in the newborn is approximately 35 mm. (b) The length of five vertebral bodies in the 6-month-old child is approximately 47 mm

Table 3 How long is a long gap?

AD Santos (1983): 2.5–4.5 cm (EA with lower fistula)
S Hagberg (1986): >2 cm under tension = 100% complications
EM Boyle Jr. (1994): >2.6 cm is long gap and >3.5 cm = ultra-long gap
AK Brown (1996): >3 cm during surgery under normal conditions
N Myers (1997): all babies without a lower fistula
P Bagolan (2004): > 3 cm or ≥3 cm vertebral bodies
L Spitz (2009): >4 vertebral bodies under tension = > 4.0 cm
CJ Hunter (2009): Any distance too wide to perform a primary repair

2. Delayed anastomosis and longitudinal bougienage

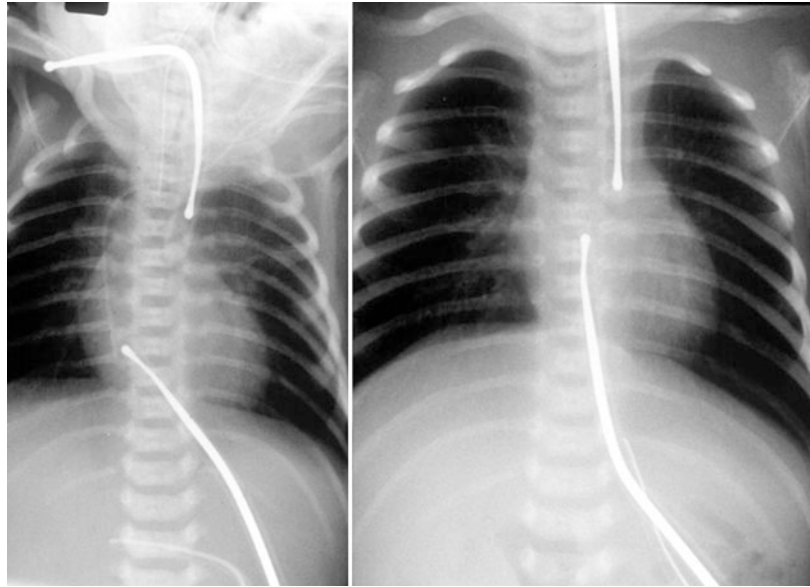
Bougienage of the esophageal segments as a stimulus for growth, additionally to the effects of the swallowing reflex and gastric reflux is a further option aimed to reduce the time till the anastomosis is possible. The bougienage of the upper pouch has first been reported by Howard and Myers (1965). Many further publications followed supporting this technique (Mahour et al. 1974). In 1966,

Lafer and Boley reduced the waiting period to 6 weeks by bougienage of the upper and lower esophagus (Lafer and Boley 1966). Technical modifications have been published by Hendren and Hale (1976) using electromagnetic devices for the longitudinal bougienage. Recent experience shows that daily bougienage of the upper and lower pouch for a few minutes within the incubator and under light sedation allows to achieve an overlap of the segments on the X-ray within 3–4 weeks until the anastomosis can be performed (Fig. 7). Although not widely accepted as a useful method, the experience shows that the time span till an anastomosis is performed can be significantly reduced and secondary resection are rarely needed.

3. Forced traction methods

Extensive tension at the anastomosis can lead to severe leakage or even disruption of the esophageal segment. To circumvent this problem – but still to be able to perform an anastomosis and preserving the child’s own esophagus – forced traction methods have been developed. Rehbein was the first to publish a method of intraesophageal forced

Fig. 7 Longitudinal bougienage of the upper and the upper and lower esophageal pouch (metal probes within plastic tubes). A near overlapping of the esophageal segments was achieved within 3 weeks



traction by means of silver olives in each segment which are pulled together along a nylon thread (Rehbein 1976). A nearly identical procedure with Teflon balls instead of silver olives was proposed by Harrison (2010). Originally the thread was inserted into the esophageal segments by thoracotomy, later this procedure was performed endoscopically (Booss et al. 1982). The aim of the technique was to bring the two segments together and to create an autoanastomosis within 10 days. The resulting stenosis needed long-term bougienage and in 50% secondary resection. Recently, a similar technique creating an autoanastomosis by means of a thread was successfully applied in five patients (Stringel et al. 2010).

In contrast to the internal traction method, an external traction technique was introduced by Foker et al. (1997). During thoracotomy, tissue-pledgetted traction sutures are placed extramucosally in the upper and lower segment and brought out to the skin below and above the incision. Daily external traction of these sutures brings the segments together within 14 ± 2.9 days and the anastomosis can be performed by a second thoracotomy. Recently, even a thoracoscopic elongation of the esophagus was successfully performed, thus

avoiding the two routine thoracotomies (van der Zee et al. 2007). According to Foker, the technique successfully elongates esophageal segments which are separated even by ultralong gaps up to 12 cm. However, the complication rate is significant: in 28.5% of 42 patients additional rethoracotomies were needed due to pulled out traction sutures, replacement of traction sutures, or adhesions, and in two out of ten patients a secondary resection of the anastomosis was performed due to stenosis (Foker et al. 1997, 2009). A recent survey of 88 international surgeons showed that 39% are using the Foker technique, but 24% of those were not satisfied with the results (Ron et al. 2009).

In 1994, Kimura and Soper developed a technique of extrathoracic elongation of the upper pouch. First, a right-sided esophagostomy is created in patients with a long-gap atresia. This stoma is advanced subcutaneously after 2–6 months several times until the proximal esophagus is long enough. In 12 patients, a final anastomosis was possible after 30 months (range 13–61 months); none of them needed a rethoracotomy or secondary replacement. In three patients the procedure was performed thoracoscopically (Tamburri

et al. 2009). Experiences of combining the Foker technique with Kimura's method resulted, however, in a high complication rate (Sroka et al. 2013).

4. Esophageal replacement

It is generally accepted that the preservation of the child's own esophagus is the preferred method. With the development of sophisticated techniques, the need to replace the esophagus is becoming rare. However, there are patients in whom substitution of the esophagus is required either because the distance between the segments is too long or the primary procedure failed. For esophageal replacement there are five options: reverse or isoperistaltic gastric tube, colon interposition, jejunal interposition, and gastric pull-up. Today is no agreement on a single organ or a single route. While gastric tubes or free and pedicled or free transplanted jejunal tubes are used in some centers only, more accepted techniques are colon interposition and gastric transposition (Spitz and Coran 2012). A detailed overview of the different replacement techniques has been published by Loukogeorgakis and Pierro (2013). A recent meta-analysis including 470 patients showed that the colon interposition has been used in 73%, gastric pull-up in 26%, and jejunal interposition in 6% (Gallo et al. 2012). According to this analysis, the colon interposition and the gastric pull-up are comparable in regard to postoperative mortality (4 and 9%), anastomotic complications (16 and 18%), anastomotic leaks (17 and 31%), and graft loss (4 and 5%), respectively. A disadvantage of the colon interposition comes from the fact that the colon has no propulsive peristalsis and the passage of ingested food is entirely by gravity. A typical complication is then an intrathoracic redundant colon with delayed emptying and unpleasant stasis of ingested food. Typical complications of the gastric transposition are anastomotic leaks or strictures and ulcers, delayed gastric emptying, and occasionally dumping syndrome.

To conclude in regard to the long-gap problem, many different strategies and techniques have been reported, but so far no consensus has been achieved which method is to be preferred. There is definite lack of prospective studies between centers, which should be based on the same categorization of cases and the use of a comparable technique measuring the distance between the esophageal segments.

Complications

Today, a newborn with esophageal atresia is diagnosed in most centers shortly after birth by the probe test thereby preventing an early pneumonia and aspiration after milk feeding. Additionally, surgical techniques have been refined, and the quality of the suture material is significantly better than in the past. Finally, the progress in pre- and postoperative care as well as excellent anesthesia techniques, intraoperative survey, and postoperative pain control contribute largely to excellent outcome rates in the Waterston A and B groups. Long-term survival rates are around 95%, and mortality is related to extreme prematurity and to major associated cardiac malformations.

However, there are a large number of early and late complications which need special care and attention.

Early Complications

The incidence of early complications has been reduced significantly in the last few decades. Not surprisingly, they occur significantly more often in babies with perioperative problems and in long-gap cases with increased tension at the anastomosis (Castilloux et al. 2010; Mortell and Azizkhan 2009; Friedmacher and Puri 2012). They include minor anastomotic leaks which occur in 6–28% in long gap cases. An esophagogram with water soluble contrast material may show a tiny fistula from the anastomosis indicating the anastomotic leak. If the patient's condition is stable, oral feeding is possible because spontaneous closure of the fistula can be expected. The early sign of larger

fistulas is the excretion of saliva through the thoracic drain. In these cases, oral feeding is postponed until the radiological control shows the closure of the fistula. Most of them will heal spontaneously. Major leaks (3–5% up to 25% in long gap cases) with subtotal anastomotic insufficiency create a life-threatening problem. Very early reoperation might be helpful, but excluding the esophagus by esophagostomy and a gastrostomy can be lifesaving.

An early but fortunately rare complication (5–10%) is the *recurrence of the tracheoesophageal fistula* (Bruch et al. 2010; Kovesi and Rubin 2004). It follows usually a significant anastomotic leak and/or juxtaposition of the esophageal and tracheal suture line, respectively. In larger fistulas, air bubbles are coming out of the drain. On the thoracic X-ray, a pneumothorax and a more or less extensive shadow can be recognized. Small fistulas are often diagnosed later when symptoms of coughing, choking, and aspiration occur during feeding. A spontaneous closure cannot be expected. Early open surgical closure of the fistula is not easy due to the local inflammatory process and a reduced tissue quality. Additionally, either a large pleural flap from the mediastinum or a vascularized pericardial flap should be interposed between the trachea and the esophagus. Addition of fibrogen glue may also be helpful. Nevertheless, the surgical procedure is associated with a significant morbidity and failure rate (Lal and Oldham 2013). Thus, tracheoscopic strategies closing the fistula from the internal site have gained popularity. They are successful in small fistulas, but several endoscopic sessions are often necessary. The strategies consist of filling up the fistula either with synthetic tissue adhesives or fibrinogen. Since the adhesives easily glide into the esophagus due to the shortness of the fistula, additional destruction of the epithelial layer either with diathermia or laser, mechanical abrasion or sclerosants, and subsequent use of tissue glue is advised (Lal and Oldham 2013).

An *anastomotic stricture* is a common finding. The typical caliber difference of the esophageal segments shows in the esophagogram often a mild

narrowing at the anastomosis. This finding is different from a true stenosis, and in most cases, oral feeding is tolerated without symptoms. Real stricture development might be a consequence of too many anastomotic sutures or anastomosis under tension, both impairing the local circulation or an anastomotic leak. Recurrent exposure to acidic reflux aggravates the stricture development (Parolini et al. 2013). A true cicatricial stenosis (30 up to 57% after a long gap) does not improve spontaneously and causes earlier or later a significant feeding problem. Minimal stenosis can be treated successfully with one to three careful dilatations – to avoid esophageal rupture. In the first line, balloon dilatations as well as proton pump inhibitor therapy are needed. In refractory cases, intralesional steroid injections or local application of Mitomycin additionally to the dilatations may be helpful. Recently, covered esophageal stents are used but proper location, tolerance by the patient, and possible migration of the stent are typical problems (Lévesque et al. 2013).

Late Complications

The most common late complication in nearly half of all patients with esophageal atresia is *gastroesophageal reflux* that may lead to chronic esophagitis and Barrett esophagus (Schneider et al. 2013, 2016; Tovar and Fragoso 2013). Severe reflux may cause feeding problems, vomiting, reduced weight gain or dystrophy, and/or due to night time aspiration recurrent respiratory tract infections. The causes of reflux are multifactorial and include developmental neuronal dysfunction in the lower esophagus, effects of the surgical mobilization of the lower pouch, and the vagal innervation as well as disturbance of the esophagogastric junction and the Hiss angle. Thus, reflux is very typical when the lower segment of the esophagus had to be pulled-up to be able to perform a primary anastomosis.

An additional complication is *dysmotility*. Propulsive peristalsis in the lower segment of the esophagus is disturbed or missing while

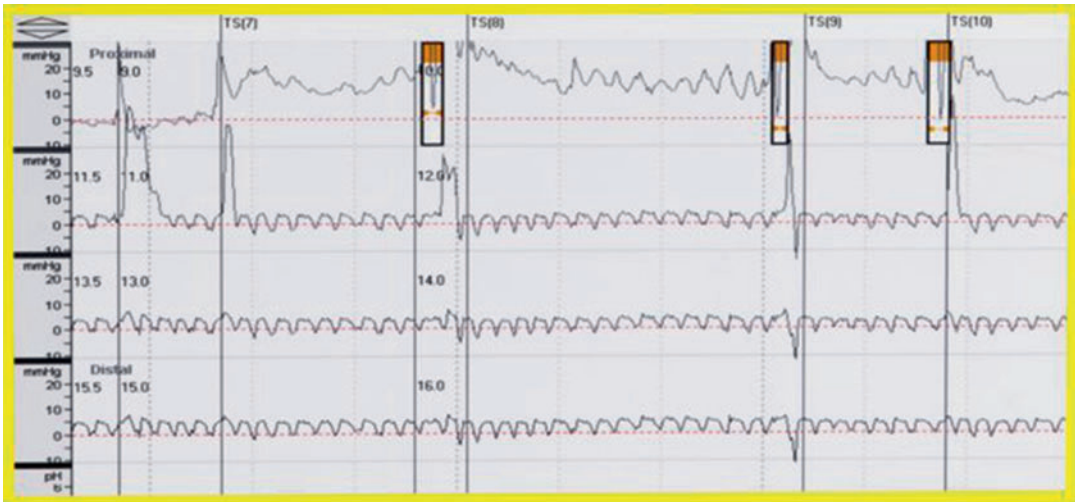


Fig. 8 Typical manometric result in a child after esophageal atresia repair: normal propulsive peristalsis in the

upper esophagus but only weak and simultaneous contractions in the lower esophagus

peristalsis in the upper esophagus till the anastomosis is often normal (Fig. 8). Recent investigations showed a significant lower density of interstitial cells of Cajal in the esophagus (Midrio et al. 2010). In 80% of the patients, the dysmotility causes a prolonged clearance time of the refluxed material. In contrast to otherwise normal babies, there is no chance for spontaneous maturation of the disturbed esophageal function. Chronic exposure of the anastomosis to refluxed gastric acid is known as trigger of refractory stenosis at the anastomosis and chronic esophagitis. Whether initially proton pump inhibitor therapy is useful to prevent stricture is a matter of debate (Hagander et al. 2012). However, up to 50% of all patients with esophageal atresia need finally a fundoplication (Tovar and Frago 2013).

Tracheomalacia is a common finding after esophageal atresia patients with lower fistula. The weak part of the trachea is in the region of the former fistula. It causes a typical barking cough and an inspiratory stridor, which is in most cases self-limiting after a few months. However, severe forms of tracheomalacia may lead to respiratory insufficiency, apneic spells, and to sudden infant death syndromes. In these cases, an aortopexy is the most often performed

procedure, either by an open approach or by thoracoscopy with a more than 80% success rate (Torre et al. 2012). An alternative is the use of a metal stent to stabilize the trachea (Fig. 9). The stent is introduced endoscopically and the respiratory problems are normalized immediately. However, if the stent is not dilated sufficiently, recurrent granulation tissue is a typical complication due to the movements of the stent relative to the trachea. In contrast, if the stent is in a firm contact with the trachea, the mucosa tends to grow over and removal after the period of a few months may be difficult. Different types of stent are today available, but experience to use them is still small.

Long-Term Follow-Up

Long-term *respiratory problems* and recurrent respiratory tract infections are reported in 40–60% and may be associated with reflux driven microaspirations or tracheomalacia (Pedersen et al. 2017; Ijsselstijn et al. 2013). Abnormal airway reactivity is often associated with atopy but only in 15% compatible with asthma. (Kovesi 2013; Sistonen et al. 2011). Pulmonary function tests showed obstruction in 21%, restriction in



Fig. 9 A Palmaz-stent used for severe tracheomalacia with life-threatening spells. The stent stabilized the trachea immediately and was removed after 8 months

21%, and both in 36% of patients (Sistonen et al. 2011).

Symptoms of *dysphagia* are reported in 38–85% of patients and only 19% have been described as free of digestive symptoms after 10–20 years (Mahoney and Rosen 2016; Legrand et al. 2012). Swallowing disorders are reported often but most patients learn to cope with this problem and are used to drink fluid together with their meals as soon as they feel that a bolus does not pass easily through the esophagus.

Chronic reflux is common and may recur after fundoplication. Symptoms in adults are usually rare and therefore chronic esophagitis may exist for a long time. The incidence is up to 19% in patients accepting regular endoscopy (Maynard and Bouin 2013). Chronic reflux may finally lead to intestinal metaplasia and Barrett esophagus with the risk of esophageal cancer. So far, eight cases of adenocarcinoma in patients with esophageal atresia and distal fistula have been collected from the literature by Rintala and Pakarinen (2013). Routine follow-up endoscopies with extensive biopsies are recommended on all adult patients (Table 4).

Spinal abnormalities exist in a significant number of adult patients. Vertebral anomalies have been detected in 45%, most often vertebral fusions, and scoliosis in 56%, being 13-fold higher when compared with healthy population (Sistonen et al. 2011). In this study, radial ray anomalies have been found in 25%, shoulder asymmetry in 80%, chest wall deformities in 15%, and rib fusion in 30% of patients.

Quality of life investigations show that the QoL score is significantly lower when compared with healthy children. The factors associated with lower scores are prematurity, barking cough, and gastroesophageal reflux disease (Legrand et al. 2012). In adult atresia patients, health-related quality of life is generally normal, but in 15% gastrointestinal or respiratory disorders may impair quality of life (Ijsselstijn et al. 2013). In another study, patients reported significantly decreased general health perception and increased bodily pain, but health-related quality of life was nearly comparable with the healthy controls; age and associated anomalies predicted poor gastrointestinal QoL, and associated anomalies and tracheomalacia predicted poor respiratory symptoms QoL (Sistonen et al. 2011). In a previous study of the same institution, adults with esophageal atresia achieved a gastrointestinal QoLI score similar to healthy controls and there was no difference in health-related QoL despite that the patients had more dysphagia and reflux and a lower respiratory symptom-related quality of life (Koivusalom et al. 2005).

In conclusion, neonates with esophageal atresia have an excellent prognosis if no severe additional malformations are present. Still a problem exists in babies with a long gap atresia and the ideal method has not been found, so far. Both strategies, to preserve the patient's own esophagus or to replace the organ have significant morbidities and more long-term complications. More prospective studies are needed to compare the different techniques based on equal data and statistics. In general, the today's outcome for neonates with esophageal atresia is excellent due to a very low mortality and an acceptable esophageal function enabling full oral nutrition and a quite good quality of life.

Table 4 Follow-up controls. Long-term follow-up strategy proposed by Rintala and Pakarinen (2013)

Findings at surveillance upper endoscopy at 15 years	No findings	Any of the following: 1. Erosive esophagitis 2. Gastric (columnar) metaplasia 3. Esophageal stricture 4. Tracheoesophageal refistula 5. Severe GER symptoms 6. Continuous GER medication	Barrett no dysplasia	Barrett with dysplasia
Next surveillance upper endoscopy	30 years	Repeat after 5 years	Repeat after 1 year	Confirm dysplasia grade and consider local or operative ablative treatment
	40 years			
	50 years			
	60 years			

Conclusions and Future Directions

Esophageal atresia is still today one of the challenges in newborn surgery. A primary anastomosis can be achieved in most of the children, even in cases of a long distance. However, prospective, multicenter studies are needed in order to evaluate the best surgical procedures for babies with very long distances between the segments. The establishment of international registries will be helpful to compare results in between institutions. Finally, long-term follow-up of all esophageal atresia patients are important due to the common reflux, the motility disorders of the distal esophagus, quality of life studies, and the impact of associated malformations.

Cross-References

- ▶ [Embryology of Congenital Malformations](#)
- ▶ [Epidemiology of Congenital Malformations](#)
- ▶ [Esophageal Replacement](#)
- ▶ [Gastroesophageal Reflux and Hiatus Hernia](#)
- ▶ [Long-Term Outcomes in Newborn Surgery](#)
- ▶ [Prenatal Diagnosis of Congenital Malformations](#)

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