REVIEW ARTICLE

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Guidelines for treatment of esophageal atresia in the light of most recent publications

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

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ABSTRACT:

Introduction: Esophageal atresia is a congenital anomaly well known in the community of pediatric surgeons. Nonetheless, some aspects of management remain vague and societies of gastroenterologists as well as surgeons have been gathering to determine pertinent ways to handle this condition.

Aim: To make ground for unification, the guidelines of some most important societies were compared and gathered in one review.

Material and methods: Literature review of online databases of the PubMed and the Cochrane Library with "(o)esophageal atresia", "guidelines" and "follow-up" used as keywords.

Results: Over the course of the last few years there has been a lot of effort invested in making clear and accurate guidelines for management of EA, largely with good results. In the majority of important matters, opinions of specialists were consistent or complementary to each other. Because some of them described different phases of management, gathering them together led to obtaining a bigger picture, which can help pediatric surgeons in making decisions while treating the patients with EA.

Conclusion: There is a necessity for careful following guidelines which have been changing quite fast along with new significant publications about EA. Some concerns remained debatable and their accentuation in this review was made to bring awareness to vague issues, such as postoperative antibiotic prophylaxis or duration of administering PPI. Additionally structured follow-up programs for the first 18 years and after reaching maturity should be made.

KEYWORDS: esophageal atresia, follow-up, guidelines

ABBREVIATIONS

AFP – alpha-fetoprotein
CT – computed tomography
EA – esophageal atresia
ERNICA – European Reference Network for Rare Inherited Congenital Anomalies
ESPGHAN-NASPGHAN – European Society for Pediatric Gastroenterology, Hepatology, and Nutrition-North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition
FOX – *Forkhead box*
GERD – Gastroesophageal Reflux Disease
GGTP – gamma-glutamyltranspeptidase
INoEA – International Network of Esophageal Atresia
MRI – magnetic resonance imaging
NGT – nasogastric tube
PPI – proton pump inhibitors
SIVI – Italian Society of Videosurgery in Infancy
TEF – esophageal atresia with tracheo-esophageal fistula
USS – ultrasound scan

INTRODUCTION

In esophageal atresia (EA) with or without tracheo-esophageal fistula (TEF) the continuity of the esophagus is interrupted and inappropriate connections may develop between the lumen of the esophagus and the trachea. EA occurs with an incidence of approximately 1 in 2.500–3.500 births [1–4]. It may manifest as an isolated anomaly, but in approximately 50% of cases it is accompanied by other congenital defects, most frequently cardiovascular (29% of children with EA), anorectal (14%) and genitourinary (14%) malformations [1, 5]. Besides being one of the congenital anomalies repaired in many centers of pediatric surgery, some aspects of the management of EA remain vague and societies of gastroenterologists as well as surgeons have been gathering to determine pertinent ways to handle this condition.

MATERIAL AND METHODS

We gather guidelines from most recent publications to deepen knowledge and create ground to unification in management of EA, focusing on the guidelines of European Reference Network for Rare Inherited Congenital Anomalies (ERNICA), both from 2019 and 2020, European Society for Pediatric Gastroenterology, Hepatology, and Nutrition-North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN-NASPGHAN) from 2016, International Network of Esophageal Atresia (INoEA) from 2017 and Italian Society of Videosurgery in Infancy (SIVI) from 2019. Additionally, the review includes information gained due to online databases of the PubMed and the Cochrane Library. Articles published in the recent 5 years were taken into consideration.

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RESULTS AND DISCUSSION

Classification

The first EA classification was made by Vogt in 1929 and is still used today. Other classifications, made by Gross, Ladd and Kluth, are further modifications of Vogt's work [3, 6]. Differences and similarities between them are shown in Fig. 1.

The most common version of EA is atresia with distal TEF (Vogt IIIB/Gross C type) [3]. In this type, and also in EA without fistula (Vogt II/Gross A type) proximal part of the esophagus ends blindly in the mediastinum, usually at the level of the 3rd/4th thoracic vertebra in Vogt III B type and higher, at the level of the 2nd thoracic vertebra in Vogt II type. Thickened wall and dilated lumen of the terminal part of the proximal segment of the esophagus creates the "upper pouch sign" in diagnostic imaging [7]. Distance between disconnected parts of the esophagus is variable and determines whether a primary reconstruction is possible. TEF without atresia (Vogt IV/Gross E type) is often called an "H-type" atresia, because of its visual similarity to the letter "H". There is a fistulous tract, which can be very narrow and is commonly located in the lower cervical region. It is usually one fistula, but cases of multiple fistulas have also been described [8, 9]. In EA with proximal TEF (Vogt IIIA/Gross B type) fistula is placed usually 1–2 cm above the end on the anterior wall of the esophagus. EA with both proximal and distal TEF (Vogt IIIC/Gross D type) is often misdiagnosed and managed as proximal atresia and distal fistula. Nowadays, with increasing use of preoperative endoscopy "double" fistula is recognized earlier and can be repaired in the initial procedure [3]. To the best of our knowledge, there has not been yet described any case of total esophageal aplasia – Vogt I type.

Clinical symptoms and diagnosis

EA is usually diagnosed within the first 24 hours after birth [10]. It should be suspected when a neonate is choking, frothing, salivating excessively and presents with respiratory distress [5, 11]. If EA is diagnosed, it is unable to reach further than approximately 9–12 cm down the esophagus using the nasogastric tube (NGT), and the plain chest X-ray shows NGT distal end stuck in the blind-ended part of the esophagus. Thin-caliber tubes might curl up in the upper pouch or pass through proximal and distal fistula and give the false impression of preserved continuity of the esophagus [4]. To prevent this situation French gauge 10 NGTs (or 8 if infants weigh less than 1500 gram) [11] are preferred. Presence of a gas bubble inside the stomach suggests distal TEF [5]. Isolated TEF (Vogt IV/Gross E type) might be overlooked and cause recurrent pneumonia and aspiration [3, 5].

Nowadays, hardly 24.3% of cases of EA are diagnosed antenatally. Only 17.9% of the most common Gross C type atresia cases are detected before birth. The effectiveness of prenatal diagnostics is the highest in Gross A type – 82.2% are revealed in utero [12]. Prenatal diagnosis depends on visualizing dilated upper blind end of the esophagus or a small or absent gastric bubble with the ultrasound scan (USS) [3]. Combination of polyhydramnios and absent or small gastric bubble in USS after the 18th week of gestation can provide sensitivity of 42% and positive predictive value at the level of 56% [13]. However, this sign is no longer present in EA with distal TEF when connection between the amnion and the fetal stomach is preserved and the stomach can be filled with amniotic fluid. Stomach bubble is also possible to be filled with gastric secretion and visible in the prenatal USS in fetuses with EA without TEF [14]. Magnetic resonance imaging (MRI) can improve positive predictive value up to 83% among patients with a high risk of EA detected during USS [15]. Detection of esophageal pouch or tracheal bowing in functional MRI is useful for diagnosis of EA. Imaging of the lower esophageal lumen is a good sign of TEF [16]. Apart from imaging option it is also a biochemical approach to uprate prenatal diagnostic efficiency. It showed a meaningful difference for total protein, alpha-fetoprotein (AFP), gamma-glutamyltranspeptidase (GGTP) and EA index (AFP multiplied by GGTP) between EA cases and other patients [17].

Preoperative management

It is necessary to consider the occurrence of EA when some other structural abnormalities are present in imaging examination, especially the components of associations like VACTERL or CHARGE. Also, finding EA manifestations in antenatal diagnosis should sensitize physicians to possible coexistence of other congenital defects [12].

A standard procedure before surgery is chest and abdominal X-ray [18, 19]. Preoperative tracheobronchoscopy is mandatory and usually informs about the location of a proximal or a distal fistula [20] and abnormalities of the respiratory tract, such as tracheobronchomalacia, change in vocal cords, cleft of airway [21, 22]. Furthermore, during tracheobronchoscopy the problems with air leakage in distal TEF can be averted by Fogarty balloon insertion [20]. Unfortunately, according to SIVI, in Europe tracheobronchoscopy is performed before operation only in 43% of cases [23].

In 13.2% to 42% of cases EA can be associated with congenital heart disease [24] and the most recent guidelines of ERNICA showed that echocardiography should be performed in every case. The important part of this diagnostic stage is taking a right descending aorta out of equation [19]. It is a relevant change to previous publications which claimed two-dimensional echocardiography did not have to be performed routinely because of sufficient exclusion of heart problems with physical and radiological examinations [24].

Preoperative three-dimensional computed tomography (CT) reconstruction can identify the exact location of TEF in approximately 80% of cases, but radiation increases the risk of future cancer and morbidity, e.g. apnea. Furthermore, CT results usually do not change the treatment plan, so this examination is not performed routinely [25].

Opinions about preoperative antibiotic prophylaxis are divided: some studies show it as an important component of treatment, which concerns 98% of children [18]. However, according to ERNICA, every case should be considered independently and there is no rush in administering prophylaxis [19]. Ventilation or intubation should be used carefully and only when needed, e.g. in case of low birthweight or premature delivery. Intubation is preferred over noninvasive ventilation [18, 19]. Continuous Positive Airway Pressure should be avoided whenever possible [23].

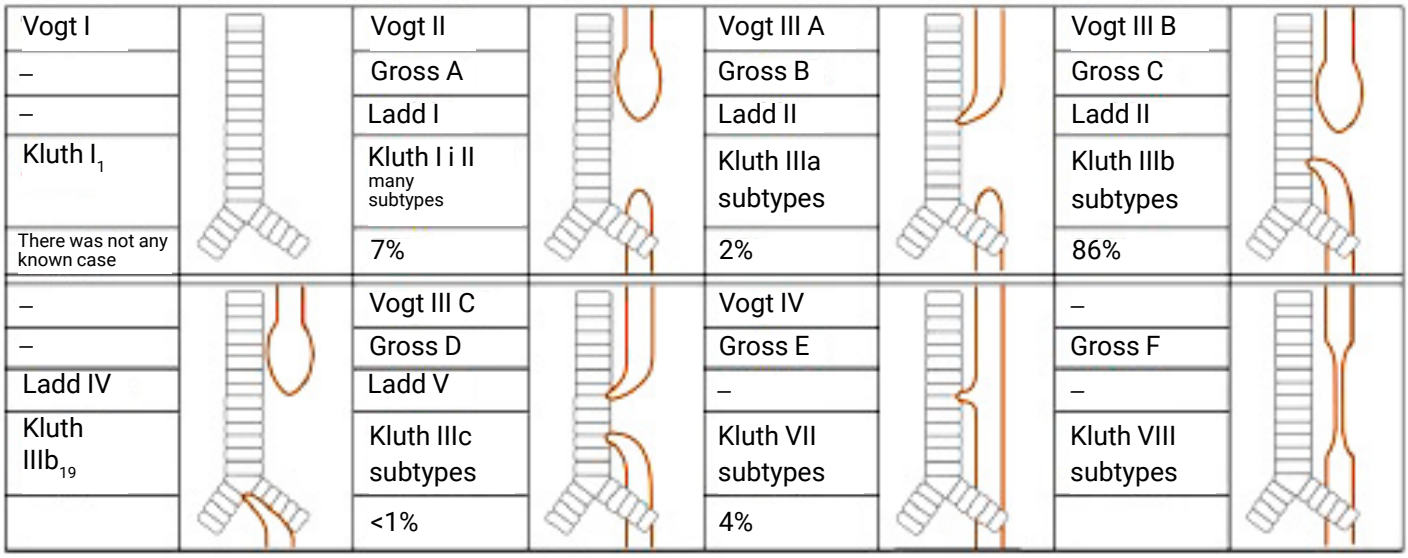

Fig. 1. Differences and similarities between Vogt, Gross, Ladd and Kluth classifications of EA (based on: Spitz L.: Esophageal atresia. Orphanet J Rare Dis, 2007; 2: 24). Reference for Fig. 1.: Tokarz A., Rogula W., Tokarska K., Tarsa M., Urban W., Zbroja K., Górecki W. Adulthood of patients after oesophageal atresia repair – General Surgeon's Guide. Pol Przegl Chir, Ahead of Print, published on-line: 2021-03-25.

Intubation should be performed carefully, particularly in cases with TEF, due to the risk of gastric distension and pneumoperitoneum [26].

The decompression of the upper esophageal segment with the continuous low-pressure suction should be routinely performed with Replogle tube or NGT [18, 19]. This method is sufficient in preventing aspiration of saliva and other methods such as cervical esophagostomy should be strongly avoided [22]. Guidelines indicate the need for gastrostomy in long-gap EA, not only for enteral feeding, but also as a stimulator of stomach growth. Also sham feeding is needed in long-gap EA with delayed anastomosis [21]. Saline should be used in case of hypovolemia, whereas the solution of 5% dextrose – to maintain the volume status. Opioids should be avoided because of postponing the extubation [27]. There is no need to routinely establish a central venous line and arterial line during days preceding operation; it is enough to establish them in the operating room [19].

There are a lot of methods for measurement of esophageal gap, none of them ideal [21]. In children with long-gap EA and gastrostomy, SIVI proposed an approach performed with a French Hegar dilator which is inserted via the gastrostomy. This method not only allows to measure the gap, but also enables to check the mobility of the distal pouch. The dilator has fluoroscopic marks and can be also connected to a dynamometer which measures the elastic force needed to stretch the pouch (according to SIVI, it is proportional to approximately 200–300 grams). To obtain pertinent results, measurements should be performed with and without pressure [23].

Surgical management of EA

Surgical management of EA should be performed in specialized centers which are hospitals with at least five new cases of EA per year. They should offer high standards of medical care and presence of a multidisciplinary team [28]. If patients are stable, the operations should be performed during working hours of the week. In the perioperative time there is a necessity for administering antibiotics [19].

There are two main approaches to surgical repair of EA with primary anastomosis:

Thoracotomy

The main aim of the procedure is ligation of TEF (when present) and reconstruction of the esophageal continuity. Viable skin incisions are: horizontal, vertical and U-shaped (Bianchi) [19]. According to SIVI, the possible approach is also a small subaxillary incision which allows for good cosmesis, because with time and growth of patient the scar migrates to the axilla and is poorly visible. This is the part of the approach called mini-invasive thoracotomy [23]. Most often the right posterolateral thoracotomy is performed. When the right-sided aortic arch is present, there is a need for an analogous left thoracotomy. It is relevant to be careful to avoid muscle damage. The most recommended approach is entry through the 4th intercostal space [19]. With the preferred, extrapleural approach the posterior mediastinum is reached and azygos vein is exposed. Then, the fistula is disclosed, dissected and ligated (transfixing suture is recommended [19]). It is important to identify correctly mediastinal structures such as major bronchus or aorta to avoid their accidental dissection. Then, the upper esophageal pouch is dissected, mobilized and both pouches are sewn together with a single layer of absorbable sutures to create an anastomosis. In this case interrupted sutures are the preferred option [10, 19, 29].

It is relevant to insert a transanastomotic tube. However, there is no need for routinely placing chest drain [19]. This last statement of ERNICA`s specialists from 2020 seemed very bold – multi-institutional study of 396 patients showed that in years 2009–2014 pleural drains were used after 95% of surgeries in 11 hospitals in the USA. However, among the remaining 28 patients with no chest tube, only in one case this management turned out to be insufficient [30].

Thoracoscopy

According to the recent publication from ERNICA, thoracoscopy is a viable option in the treatment of EA. In debate on whether thoracoscopy can lead to serious pathophysiological damage,

such as acidosis (or problems with cerebral oxygenation), specialists of ERNICA took a sceptical stance and did not share these concerns [19]. Also SIVI pointed out that only a small amount of CO_2 is insufflated during the procedure and the risk of hypercapnia and related acidosis is low [23].

This approach offers multiple advantages (possibility of magnification, better cosmesis, fewer musculoskeletal deformities), but concurrently requires longer operative time experience in this field. There are colliding opinions if thoracoscopy provides faster recovery compared to thoracotomy. When it comes to technical demands, surgery cannot last longer than 3 hours and the insufflation pressure of CO_2 cannot be higher than 5 mmHg [19].

Thoracoscopic repair can be performed through a transpleural or extrapleural access. In the first case, the insufflation of the pleural space causes right lung collapse. This procedure provides a good view of the superior vena cava, azygos vein, phrenic and vagus nerves [31]. Extrapleural access is obtained by dissection of intercostal muscles and inserting the trocar avoiding the pleura. This procedure allows for insufflation of carbon dioxide to obtain an additional operative area. It is believed this approach prevents a leak to the pleural space and empyema [32].

Management of long-gap EA

According to ERNICA, the definition of long-gap EA is "any EA with a gap of three vertebral bodies or more" [21]. Furthermore, any EA combined with absence of air in the abdomen should be initially considered as a long-gap [21, 22]. The preferred method of treatment is delayed primary anastomosis, best to be performed at the age of 2–3 months. Using traction suture, placed thoracoscopically as well as in open surgery, and pouch mobilization are specified as promising, but possible to be performed only in specialized centers [21].

According to INoEA, the viable option is jejunal interposition, which allows intrinsic motility and causes less pulmonary complications than other replacement techniques [21, 22]. During this surgery vascularized stalk is used in the case of neonate, whereas microanastomosis – in the case of older children [22].

There is a possibility of gastric transposition. A possible option during this surgery is laparoscopic assistance. However, partial gastric transposition with intrathoracic anastomosis is not recommended. Furthermore, this operation should include pyloroplasty and if sham feeding does not give expected results, there is a need for jejunostomy [21].

Kimura`s method, circular myotomy and gastric division are not recommended. Colonic interposition should be avoided [21], although INoEA considers it as a last resort, concurrently indicateing its complications, such as stasis of food and inappropriate growth [22].

Postoperative management

At first feeding takes place via the transanastomotic tube. According to ERNICA it can be routinely initiated at 24 hours [19]. If there are no complications, the transanastomotic tube can be removed at 8^{th}–9^{th} postoperative day [23]. There is no need for a routinely performed contrast study before oral feeding. In case of refistula, either endoscopic or surgical revision may be introduced [19].

There is no consensus for administering antibiotics for longer than 24 hours – every case should be considered independently [19]. A study of 396 patients from eleven children's hospitals showed that in 69% of cases postoperative antibiotics were continued after the first 24 h following surgery (range among hospitals 36–97%). Only in 15% of cases the cause of administering antibiotics was an active infection [30]. Further doubts about the necessity of postoperative antibiotics were shown in a study of 292 patients treated in the USA. In 74% of cases antibiotics were administered for longer than 24 hours after surgery of EA, only in 10% the cause was active infection. However, after excluding patients with infection, there was no difference in rates of: mortality, sepsis, state of shock, organ failure or wound infection between groups of patients with or without antibiotics administered for longer than 24 hours [33]. Broad variability among hospitals suggests the necessity of a unified approach to postoperative antibiotics and not using them only as a prophylaxis for longer than 24 hours after surgery [19, 30].

Acid suppression is a very important part of hospital treatment [28]. In past publications, proton pump inhibitors (PPI) as well as H2 blockers were acceptable [30]; both ESPGHAN-NASPGHAN and ERNICA advise proton pump inhibitors [28, 34].

There is a study which showed the potential benefits of administration of glycopyrrolate in case of anastomotic leak after surgery. The study included 42 patients with leak after primary repair of EA: anastomotic leak stopped in the treatment group in 16 cases (76%), while in the placebo group only in 6 cases (29%). According to authors, glycopyrrolate reduces oral secretions and increases healing [35]. This study is also mentioned in ERNICA as demanding further research [19].

Before discharge the abdominal and renal ultrasound should be performed (if they were not performed before) [19]. SIVI also mentioned brain ultrasound [23]. The matter of utmost significance is education for parents or caregivers (including resuscitation training) [19].

Follow-up and late complications

Patients after surgical repair of EA need scheduled follow-up visits. According to ERNICA there is a necessity of:

1. Endoscopy in the first year of life;
2. Endoscopies with biopsies at the gastroesophageal junction and in the place of anastomosis. They should be performed every 5–10 years and at entry into adulthood [28];
3. Endoscopy depending on symptoms: in every case of new or worsening of the earlier symptom;
4. Lung function tests;
5. 24-h pH- or pH-impedance monitoring at discontinuation of PPI [28];
6. Bronchoscopy for symptomatic children [21].

There is no need for a contrast study to be performed routinely [28].

ESPGHAN-NASPGHAN proposed a similar scheme for endoscopy. It should be performed after discontinuation of PPI, before the age of 10 and at entry into adulthood [34]. Biopsies should be taken in accordance with ESPGHAN guidelines and made also to exclude eosinophilic esophagitis [21]. Every follow-up endoscopy of the upper GI tract should consider the need of screening for Barrett's esophagus [28, 34].

Eosinophilic esophagitis was mentioned above not without reason. It is suspected that the mutations in a gene known as the *Forkhead box* (FOX) take part in the etiology of both EA and eosinophilic esophagitis. In endoscopy it may have many presentations: from oedema, exudate to even crêpe-paper mucosa with a risk of bleeding. In 7–32% of cases, endoscopy can be normal and only the biopsy shows a higher number of eosinophils. Changes in the mucosa are not homogeneous – in literature they are described as "patchy", therefore it is important to take no less than 2–4 biopsies [36].

There are divided opinions regard the duration of acid suppression. According to ESPGHAN-NASPGHAN it should last 12 months after surgery; in ERNICA there was no consensus on this matter [28, 34]. However, a study of 396 patients with EA treated surgically showed 83% of them needed acid suppression at the time of discharge; 48% of them – one year after operation [30]. Only in long-gap EA there was no doubt on this matter: IPP should be administered for 12 months [21]. The authors of this review emphasize it is relevant to evaluate the state of the patient and the validity of administering these medications.

To diagnose anastomotic stricture, a contrast study or endoscopy should be performed [34], whereas to manage it: hydrostatic balloon or semi-rigid dilatation [28]. During anastomotic dilation airway should be protected by tracheal intubation and surgery performed under general anesthesia [34]. If stricture is recurrent, the limit of esophageal dilatations is five. Afterwards, fundoplication should be considered 28. ESPGHAN-NASPGHAN allows local use of mitomycin C and intralesional or even systemic steroids in the management of recurrent strictures [34], however in ERNICA (2019) less than half of specialists agreed with these methods of treatment and recommended mainly customized stents or indwelling balloons [28]. Interestingly, a specialist of ERNICA in an article published a year later (2020) about the management of long-gap EA, claimed that mitomycin C as well as steroids are viable options in these cases [21]. This is a remarkable example of divided opinions on the treatment of EA and guidelines which have been changing very quickly.

ESPGHAN-NASPGHAN pointed out that the decision on fundoplication should be made very carefully. In repaired EA gravity helps in the clearance of the esophagus, which is scarce because of its poor motility, and fundoplication could disturb this process [34]. Indications for fundoplication include:

1. Recurrent anastomotic strictures;
2. No improvement in the treatment of GERD, despite PPI;
3. Need for transpyloric feeding for a long time;
4. Cyanotic spells [28, 34].

Fundoplication should be preceded by a contrast study with barium, endoscopy with biopsies and 24-hour pH-metry [34].

Except for pediatric surgeons, children with EA should be seen at least by gastroenterologists, otolaryngologists and pulmonologists [34]. There is a necessity for a structured follow-up program and well-deliberated ways of transition of patients into care of specialists after they reach maturity [22].

CONCLUSIONS

The guidelines for the management of EA are still not perfect. Guidelines of ERNICA were made as statements based on voting of specialists, part of them, especially related to surgical management, being difficult to interpret. There are also a lot of debatable issues, such as postoperative antibiotic prophylaxis or duration of PPI administration. Furthermore, regardless of the official guidelines e.g. about the necessity of preoperative tracheobronchoscopy, a lot of hospitals work based on their own policy. Additionally, guidelines have been changing very quickly even within the same association; an example would be significant differences between resolutions of ERNICA from 2019 and 2020. Only deepening of specialist knowledge and unification of management can provide the best care for patients.

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