REVIEW OF OESOPHAGEAL ATRESIA AND TRACHEOESOPHAGEAL FISTULA IN HOSPITAL SULTANAH BAHIYAH, ALOR STAR 2000 - 2009

by

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(II) CONTENTS

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(V) ABBREVIATIONS

Abn.	Abnormality
ASD	Atrial septal defect
CHD	Congenital heart disease
cm	Centimetre
CT Scan	Computed Tomography Scan
Dr.	Doctor
EA	Esophageal Atresia
GIT	Gastrointestinal tract
HSB	Hospital Sultanah Bahiyah
HUSM	Hospital Universiti Sains Malaysia
Kg	Kilogram
No	Number
PDA	Patent ductus arteriosis
Pts	Patients
SHH	Sonic Hedge Hoc
TEF	Tracheoesophageal fistula
VACTERL	Vertebra (V), Atretic gut (A), Cardiac (C), Tracheoesophageal (E), Renal agenesis (R), Limb deformity (L).
VSD	Ventricular septal defect

(VI) ABSTRAK

Atresia esophageal (EA) dan *tracheoesophageal fistula (TEF)* merupakan satu anomali kongenital yang berlaku kepada bayi baru lahir dengan kejadian 1 dalam 2500 kelahiran di seluruh dunia. Terdapat 47 pesakit atresia esophageal yang dimasukkan ke HSB dari Januari 2000 ke Disember 2009, 26 (55%) lelaki dan 21 (45%) perempuan. Agihan pesakit mengikut keturunan ialah seramai 34 Melayu (72%), 9 Cina (19%) dan 4 India (9%). Daripada 47 bayi yang mengidap TEF dan EA, 36% menghidap *polyhdromnios* dalam penilaian antenatal. Terdapat hanya 3 jenis EA/TEF yang kelihatan; Jenis A (9%), Jenis C (87%) dan Jenis E (4%). Julat berat bayi tersebut adalah dari 0.8kg hingga 4.0kg. Berat timbangan bayi paling kecil yang masih hidup ialah 1.1 kg dan terdapat perkaitan signifikan dengan hasil pembedahan ($p<0.05$). Kebanyakan bayi (20) dibedah dalam masa 24 jam kelahiran. Tiada perkaitan signifikan di antara masa intervensi pembedahan dan hasil ($p>0.05$). 23 (49%) daripada mereka dilahirkan dengan kecacatan kongenital dan terdapat perkaitan signifikan dengan hasil pembedahan ($p<0.05$). Berdasarkan roentgenogram dada, 20 (43%) daripada mereka menghidap pneumonia dan terdapat perkaitan signifikan dengan hasil ($p<0.05$). Kadar kematian ialah 23% dan punca kematian ialah pneumonia yang teruk (36%), kegagalan ginjal yang teruk (18%), kecacatan jantung yang teruk (18%) dan kecacatan kongenital berbilang (28%). Pengkelasan Bremen paling sesuai digunakan dalam menentukan prognosis bayi dengan TEF dan EA di Hospital Sultanah Bahiyah, Alor Setar. Sebagai kesimpulan, hasil EA dan TEF ditentukan melalui berat lahir, kecacatan kongenital dan kehadiran pneumonia prapembedahan.

(VII) ABSTRACT

Esophageal atresia (EA) and tracheoesophageal fistula (TEF) are one of the congenital anomaly occurring in the newborns with the incidence of 1 in 2500 births seen worldwide. There were 47 patients with esophageal atresia admitted to HSB from January 2000 to December 2009, out of which 26 (55%) were males and 21 (45%) females. The distribution of patients by race were 34 Malays (72%), 9 Chinese (19%) and 4 Indians (9%). Out of 47 babies with TEF and EA, 36% of them had polyhdromnios in the antenatal evaluation. There were only 3 types of EA/TEF seen; Type A (9%), Type C (87%) and Type E (4%). The birth weight of the babies range from 0.8 kg to 4.0 kg. The smallest surviving baby weighing 1.1 kg. There was a significant association with the outcome of the surgery ($p< 0.05$). Most of the babies (20) were operated within 24 hours of presentation. There were no significant association between time of surgical intervention and outcome ($p>0.05$). 23 (49%) of them were born with congenital malformation and there was a significant association with the outcome of the surgery ($p<0.05$). Based on the chest roentgenogram, 20 (43%) of them had pneumonia with significant association with the outcome ($p<0.05$). The mortality rate is 23% and the causes of death were severe pneumonia (36%), severe renal failure (18%), severe cardiac malformation (18%) and multiple congenital malformations (28%). Bremen classification is most suitable in determining the prognosis of the babies with TEF and EA in Hospital Sultanah Bahiyah, Alor Star. In conclusion, the outcome of EA and TEF is determined mainly by birth weight, congenital malformations and presence of preoperative pneumonia.

1. INTRODUCTION

Oesophageal atresia (EA) is a congenitally interrupted oesophagus. Tracheoesophageal fistula (TEF) is a congenital or acquired communication between the trachea and oesophagus (Sharma et al. 2000). EA and TEF are among the commonest congenital anomaly occurring in the newborns, with the incidence of 1 in 2500 births (Spitz L 2006). The incidence worldwide is reducing in trend for unknown reasons (Dave et al. 1999).

Thomas Gibson first described EA and TEF in 1696. Despite the identification and description, the first successful repair was only achieved two centuries later by Ladd and Lever in 1939 and 1940 (Myers 1997). There are many surgical techniques used to repair TEF and EA, tested through time and adjusted to the anatomical variations the patient presents with (Krishinger et al 1999). Post-operative care is as important as the surgery itself. A good neonatal intensive care unit is a necessity to determine the success of the surgery (Sigmund et al 1989).

The outcome depends on many factors, mainly the associated congenital anomalies with the TEF. Waterston and Spitz have suggested different classifications that will determine the prognosis of the patient. These classifications are based on the birth weight, timing of surgery and associated cardiac anomaly. There is no racial predilection for this condition. EA and TEF are usually diagnosed very early in life. Currently, the survival rate is around 80 - 90% (Deurloo et al 2000).

Complications that may arise can be early and late postoperative period. These complications must be identified and treated accordingly.

Hospital Sultanah Bahiyah offers the only paediatric surgical services in the northern region. Almost all the babies diagnosed with EA/TEF in the northern region will be referred to us for further management.

This study will provide a preliminary database for the cases performed in HSB in the past 10 years. This study will also look into the outcome of babies with EA and TEF and to assess the associated risk factors influencing the outcome. Identifying the relevant risk factors in the local centre will enable us to stratify the prognosis of the babies based on suitable prognostic criteria.

It will also enable us to compare the standard of care in the management of EA/TEF between centres worldwide and assist in improving the shortcoming identified in the course of this study.

2. LITERATURE REVIEW

2.1 EPIDEMIOLOGY

The incidence of EA and TEF is 1 in 2,500 (Spitz L 2006). The incidence worldwide is in reducing trend for unknown reasons (Depaepe et al. 1993). The highest incidence reported worldwide is in Finland with the incidence of 1 in 2,500 live births. There is a slight male preponderance for the occurrence of this condition (Depaepe et al. 1993). There is also a 6% increased chance of having EA and TEF if it is a twin pregnancy. It is also reported that more than 50% of babies with EA and TEF are associated with other congenital anomalies (Ishimaru et al. 1998).

2.2 HISTORY

Before the 17th century, EA and TEF were poorly described and understood. The babies with such conditions usually die. William Durston first described the case of oesophageal atresia in one conjoined thoracopagus twin in 1670. In 1696, Thomas Gibson gave the first description of EA with a distal TEF. In 1862, Harald Hirschsprung, a famous Danish paediatrician, described 14 cases of oesophageal atresia. In 1898, Hoffman resorted to a gastrostomy after failing to anastomose the defect primarily (Myers 2006).

The initial part of the 20th century was a great challenge for the surgeons to understand the condition and to formulate a solution. It was until 1939 and 1940 when William E Ladd of

Boston and N. Logan Leven performed a staged procedure by ligating the fistula and placing a gastrostomy for feeding. The reconstruction of the oesophagus was done later and the baby survived. However, a year later in 1941, Cameron Haight of Michigan successfully repaired oesophageal atresia in a single stage primary closure with an extrapleural approach in a 12-day-old baby (Spitz 2006).

In the late part of 20th century, the survival of babies with EA and TEF improved tremendously. This could be due to early diagnosis and referral, better neonatal care facilities, good neonatal transportation system, more experienced anesthetists with modern anesthesia, more intense postoperative care and last but not least, well trained surgeons (Spitz 2006).

2.3 EMBRYOLOGY

Oesophagus

The initial stages of development are divided into the embryonic and fetal period. Beginning from fertilization up to the 9th week is the embryonic period. Subsequently is called the fetal period. In the first 2 weeks of development, the formation of the ectoderm and endoderm takes place. From day 15 onwards, the mesoderm, which will give rise to the connective tissue, angioblast, smooth muscle and serosal layer of the gut will form. While the mesoderm proliferates, the human embryo elongates cranio caudally and folds laterally. The yolk sac forms the dorsal part of the embryo and the embryo itself forms a 'body cylinder' and is divided into the intraembryonic and the extraembryonic parts. The

intraembryonic part gives rise to the digestive tract and the accessory glands. The early digestive system divides into foregut, midgut and hindgut.

The development of the gut takes place in four major axes (anterior-posterior, dorsal-ventral, left-right and craniocaudal) and is influenced by epithelial mesenchymal interactions mediated by specific molecular pathways. The oesophageal development takes places in the anterior-posterior axes and is mediated by growth factors such as Wnt5a (mesodermal protein), Six2/Sox2, Hoxa-2, 3 and 4 (endodermal proteins).

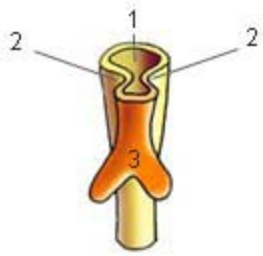
In week 4 of the development, a small diverticulum develops on the ventral surface adjacent to the pharyngeal gut. This diverticulum elongates and separates from the dorsally located foregut through the formation of the oesophageal tracheal septum and become the primitive respiratory tract. The rest of the foregut develops rapidly along with the craniocaudal growth of the embryo. By the 10^{th} week, a single oesophageal lumen with a superficial layer of ciliated epithelial cells is formed. Stratified squamous epithelium begins to replace the ciliated epithelial cells during the 4^{th} month of development and this continues till birth.

Trachea

In the 4^{th} week of the development, the lower respiratory tract develops from an outgrowth of the ventral wall of the foregut, also known as the respiratory diverticulum. The epithelial lining of the larynx, trachea, bronchi and alveoli arise from the endodermal of the diverticulum. The cartilaginous component of the trachea is derived from the splanchnic

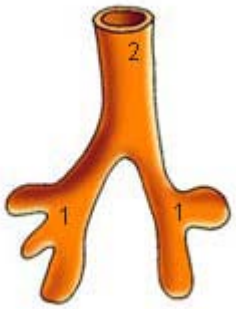
mesoderm. The elongation of the diverticulum caudally will separate it from the foregut by the oesophagotracheal septum. The initial wide communication between the foregut and the tracheal will transform into a thin T-shaped slit and then disappear (Kuo and Urma 2006).

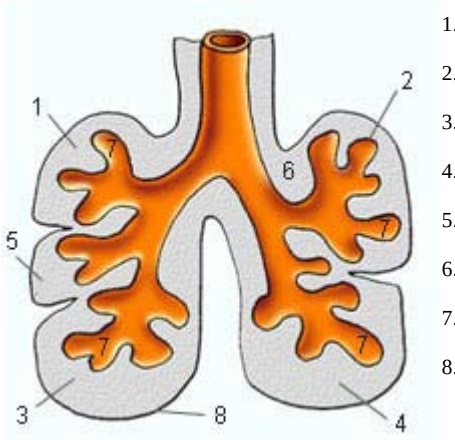
1. Foregut
2. Esophageal tracheal septum
3. Respiratory diverticulum



1. Pharynx
2. Lung buds
3. Trachea
4. Esophagus

1. Trachea
2. Lung buds





1. Right upper lobe
2. Left upper lobe
3. Right lower lobe
4. Left lower lobe
5. Right middle lobe
6. Splanchnic mesoderm
7. Bronchial buds
8. Visceral pleura

Figure 1: The Development of the Respiratory Diverticulum (Adapted from GI Motility Online by Kuo B and Urma D, 2006).

2.4 ANATOMY

Oesophagus

Oesophagus is a flattened muscular tube with the length of 18 to 26 cm, begins from the lower border of the cricoid cartilage (at the level of C6 vertebrae and the upper sphincter) and ends at the cardiac orifice of the stomach at the level of T11 vertebrae. The lumen of the oesophagus is naturally collapsed between swallows and distends to the size of 2cm anterior-posterior dimension and 3cm laterally. The oesophagus can be described in three portions, the cervical oesophagus, the thoracic oesophagus and the abdominal oesophagus.

The cervical oesophagus lies in front of the prevertebral fascia, posterior to the trachea and inclines slightly to the left of the midline when it enters the thoracic cavity. The thoracic portion of the oesophagus returns to the midline at the level of T5 vertebrae and at T7, the oesophagus deviates to the left again and pass in front of the descending thoracic aorta, piercing the diaphragm 2.5cm to the left of the midline. Throughout the length of the thoracic oesophagus, the trachea is in direct anterior relation. On the posterior plane, the oesophagus is crossed posteriorly by the hemiazygos, accessory hemiazygos and the right posterior intercostals arteries. The abdominal oesophagus turns to the left and forward immediately after piercing the diaphragm and grooves the posterior portion of the left lobe of the liver. It enters the orifice of the cardia of the stomach.

The oesophagus wall is composed of four layers. They are the innermost mucosa, submucosa, muscularis propria and adventitia. The oesophagus has no serosal layer.

The blood supply of the oesophagus is based on the different portion of the oesophagus. The cervical oesophagus is supplied by the branches from the inferior thyroid artery. The thoracic oesophagus is supplied by the paired branches of the thoracic aorta and the terminal branches of the bronchial arteries. The abdominal oesophagus is supplied by the oesophageal branch of the left gastric artery and the branch from the left phrenic artery.

The venous supply is also segmental. The veins from the proximal and distal oesophagus drain into the azygos system whereas the mid oesophagus drains into the collaterals of the left gastric vein, a branch of the portal vein.

The lymphatic from the proximal third of the oesophagus drains into the deep cervical lymph nodes and then into the thoracic duct. The middle third of the oesophagus drain into the superior and mediastinal nodes. The lymphatic flow of the distal third oesophagus drains following the left gastric artery into the gastric and celiac nodes.

The oesophagus is innervated by the sympathetic and the parasympathetic nervous system, mainly by the vagal and the spinal nerves.

Trachea

Similar to oesophagus, the trachea begins in the neck below the cricoid cartilage at the level of C6 vertebra, anterior to the oesophagus. It enters the thoracic inlet at the midline and passes downwards and backwards posterior to the manubrium. At the level of the T5 vertebra, the trachea bifurcates into two main bronchi. The entire length of the trachea is 10cm long with the diameter of 2cm.

The trachea receives the blood supply from the branches of the inferior thyroid artery and the bronchial arteries. The venous drainage is into the inferior thyroid vein.

The lymphatic channels pass into the pre and paratracheal nodes and to the inferior deep cervical nodes.

Tracheal nerve supply is derived from the vagus and the recurrent laryngeal nerve forming the parasympathetic portion. The smooth muscle and the blood vessels is supplied by the sympathetic fibres from the sympathetic trunk (Sinnathamby 2006).

2.5 PATHOPHYSIOLOGY

The trachea and oesophagus are very closely related from the early phase of embryonic life. The development and separation of these structures are believed to be from apoptosis, which causes collapse and fusion of the lateral walls of the foregut. Any point along the foregut that fails to achieve this will have a remnant septum that will form fistulous tract between the trachea and oesophagus (Dave et al. 1999).

To understand the pathophysiology of EA, three separate studies were carried out. They are the:

1. the ontogeny of peptide innervation of the oesophagus;

2. studies on the adriamycin rat model

3. studies on the recently developed adriamycin mouse model

Hitchcock et al was responsible to investigate on the ontogeny and distribution of neuropeptides that influences the growth of nerve cells density and myenteric fraction of the esophagus. He discovered the density of these cells will peak at 16 to 20 weeks of gestation, which is around the time the fetal swallowing first occurs in utero.

Cheng et al discovered that the immunoreactvity for S100 and galanin were significantly elevated in rats treated with adriamycin. His postulation was that the abnormal distribution of the nerve tissue in the atretic esophagus contributes to the dysmotility even after the corrective surgery.

Subsequently, Ioannides et al created and adriamycin model of EA in the mouse because there were greater availability of molecular probes and genetic strains in the mouse than rats. He showed that in the absence of tracheoesophageal separation, the dorsal fistula retains its non respiratory commitment, that is, is of foregut origin and stains negative for Nkx2.1, a marker for respiratory elements. He also showed that sonic hedgehog gene (Shh) expression undergoes a reversal in the dorsoventral patterning during tracheoesophageal separation. This dorsoventral patterning is disturbed in the adriamycin mouse model of EA. However, despite all these studies, there are no babies with EA and TEF were documented to be exposed to adriamycin (Yagyu et al. 2000).

EA could also be due to the dysfunction of the active cellular proliferation where the laryngotracheal tube grew faster than the oesophagus so that if separation of the oesophagus and trachea was slightly delayed, the faster growing trachea would separate the proximal and distal oesophagus. This will lead to a fistulous formation.

Till today, the cause of EA or TEF is unknown. There are no known human teratogens known to affect the foetus. There are many postulations about the genetic predisposition of EA and TEF, but currently many authorities believe otherwise. Having twin pregnancy has been associated with 6 times more likely to have EA (Dave et al. 1999).

In 1953, Gross and Boston described EA and TEF in six different types (Smith 2006). They are as follows:-

Type A – Oesophageal atresia without fistula (pure oesophageal atresia), 10%

Type B – Oesophageal atresia with proximal TEF, <1%

Type C – Oesophageal atresia with distal TEF, 85%

Type D – Oesophageal atresia with proximal and distal TEFs, <1%

Type E – TEF without oesophageal atresia (the H-type fistula), 4%

Type F – Congenital oesophageal stenosis, <1%

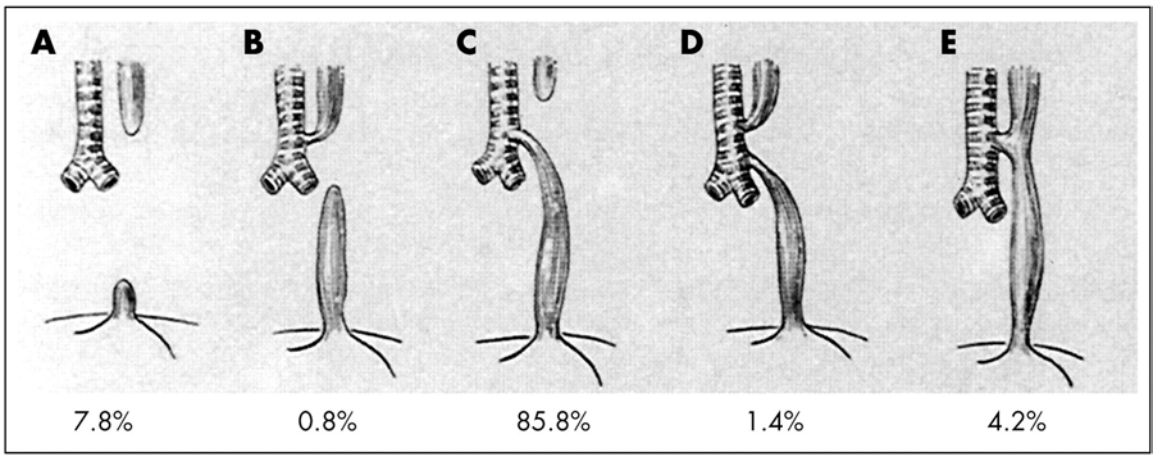


Figure 2: Anatomical variations of EA and TEF by Gross (Adapted from Oesophageal atresia, tracheo-oesophageal fistula, and the VACTERL association: review of genetics and epidemiology by Smith C.S. from Journal of Medical Genetics 2006)

Foetus affected by EA will have difficulties in swallowing the amniotic fluid, especially if the fistula is absent. Due to this incapability, the accumulated amniotic fluid will lead to polyhydromnios and subsequently into premature labour. The foetus also absorbs some amount of nutritional values from the ingestion of amniotic fluid and this could be the cause for them being small for gestational age (Spitz 1996).

Once born, the neonate will have copious amount of saliva drooling due to the inability to swallow. If the neonate is allowed to suckle, the aspiration of the milk may lead to pneumonia and will severely impair the prognosis (Agarwal et al. 1996). The air can pass down the fistula when the baby cries, strains or need to be ventilated preoperatively. This can cause severe distension of the gastric and lead to gastric perforation.

Manometric studies in babies with EA have shown dysmotility in the entire length of the oesophagus. This will cause poor propagating peristaltic waves and lead to dysphagia when the feeding starts. Due to the lower oesophageal sphincter failure in cases of EA, the incidence of gastroesophageal reflux is high. The reflux can lead to oesophageal stricture, aspiration pneumonia and tracheal collapse (Shekhawat et al. 2000).

2.6 CLASSIFICATION

There are many classifications used to estimate the prognosis. Among the most frequently referred are the Waterston classification and Spitz classification.

Waterston devised a classification system to assist in the management of EA and TEF in 1962. He classified them into three categories and is dependent on the birth weight, the pulmonary condition and congenital anomalies. Those falling in category A will undergo immediate repair, category B will be delayed repair and category C will be staged repair. As the years go by, this classification was further simplified by Randolph in 1989. He suggested a clinically helpful system that considers the physiological status to determine the surgical management. Weight, pulmonary conditions and gestational age were not considered. If the physiological parameters are promising, the baby is taken into surgery immediately. Staged repairs are only used for those severely compromised babies, especially those with severe cardiac abnormalities (Deurloo et al. 2004).

At a later period, in 1994, Spitz suggested a new classification system after reviewing 387 babies. He observed that the main prognostic factor in determining the outcome is actually the status of the cardiac disease. He divided the babies into 3 groups, similar to Waterston but only based on the birth weight and the presence or absence of cardiac disease (Okamato et al. 2009). Yagyu et al. suggested a modification to the Spitz classification, Bremen classification, in 2000 by adding on the preoperative pulmonary status, which better predicts the prognosis of the babies (Yagyu et al. 2000).

Table 1: Prognostic classifications of EA and TEF (Spitz et al. 1993), (Deurloo et al. 2004) and (Eradi et al. 2003).

Waterston Classification (1962)	Spitz risk groups (1994)	Bremen Classification (2000)
A. Birth weight > 2500g No pneumonia No anomalies	Group 1 Birth weight >1500g No congenital heart disease	Group 1 Birth weight >1500g No congenital heart disease No pneumonia
B. Birth weight 1800 – 2500g Moderate pneumonia or anomalies.	Group 2 Birth weight < 1500g or congenital heart disease	Group 2 Birth weight < 1500g or congenital heart disease or pneumonia
C. Birth weight < 1800g Or Birth weight >1800g with severe pneumonia or severe anomalies.	Group 3 Birth weight < 1500g and congenital heart disease.	Group 3 Birth weight < 1500g and congenital heart disease or pneumonia

The survival rate based on the Waterston classification Group A, B and C are 99%, 93% and 71% respectively. The Spitz Group 1, 2 and 3 have the survival rate of 97%, 59% and 22% (Deurloo et al. 2000). These classifications are only to assist physicians to compare results in an organized and meaningful way and not to make clinical decisions based entirely on it. Each baby must be individualized in their treatment (Spitz et al. 1993).

In developing countries, the survival rate depends not only on the mentioned factors, but also on the timing of the referral, hypothermia and high rate of pneumonia. Many babies born in the outskirts will have delayed referral to the tertiary centre because of the lack in experience in making the diagnosis upon delivery (Agarwala et al. 1996).

2.7 PRESENTATION

Mothers delivering babies with EA can be complicated with polyhdromnios during their pregnancy. This happens in 33% of the mothers carrying babies with EA and TEF. It happens in 100% of cases with only atresia without fistula (Spitz et al. 1993). Polyhdromnios will lead to premature delivery and worsen the prognosis (Saxena 2008). Antenatal suspicion will ensure the mother delivers in a tertiary centre where there is a paediatric surgical service and neonatal medical services.

Babies born with EA and TEF will have drooling salivation. Noting this, a nasogastric tube should be inserted and if the tube coils in the cervical oesophagus (around 10cm from the upper gum), then it is highly suggestive of EA. Risk of aspiration pneumonia is increased due to this. It is important to ensure the saliva is continuously cleared from the oral cavity by the nursing staff or by using the Replogle suction tube on continuous low pressure suction in the upper pouch (Dave et al. 1999). Besides salivation, babies fed after delivery will develop respiratory distress and aspiration pneumonia. A chest and abdominal x-ray is performed to look for the coiling of the nasogastric tube and also to identify the presence of bowel shadows. Absence of bowel shadow may suggest there is no fistula (Type A or B) and vice versa. In Type A or B, a preoperative bronchoscopy may assist in determining the presence of proximal fistula. Oesophagogram is not necessary in the diagnosis (Dave et al. 1999).

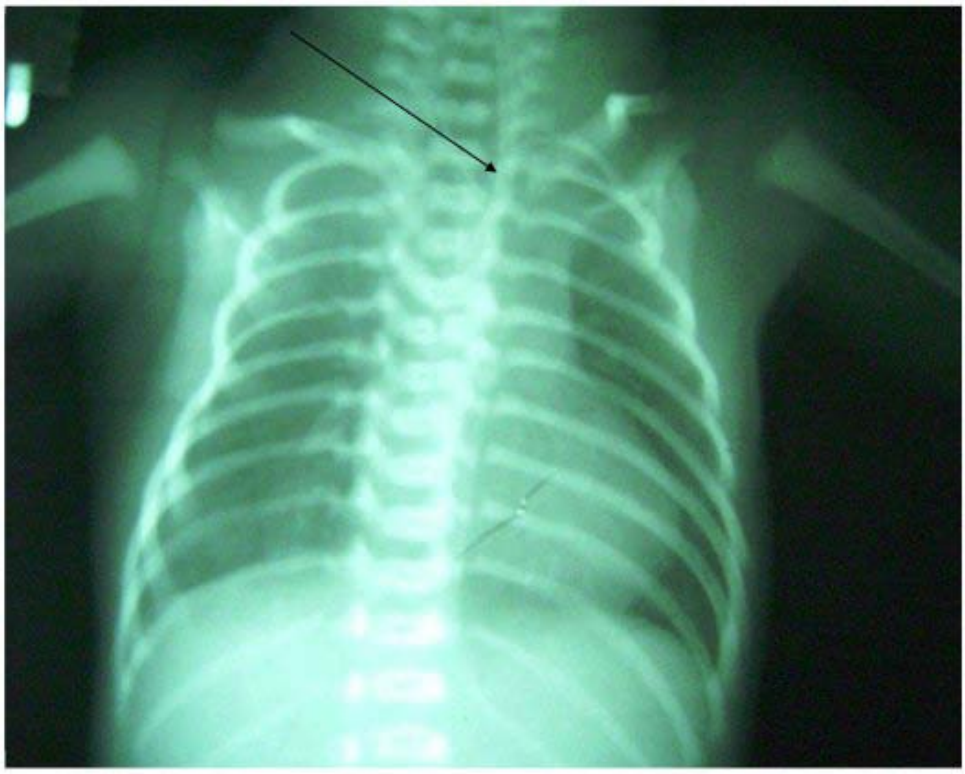


Figure 3: Plain roentgenogram of chest showing coiled nasogastric tube and gasless abdomen (Adapted from Esophageal Atresia with Distal Tracheoesophageal Fistula with Gasless Abdomen: A Diagnostic Dilemma by Hassan Z, Upadhyaya V and Gangopadhyay A from The Internet Journal of Pediatrics 2009)

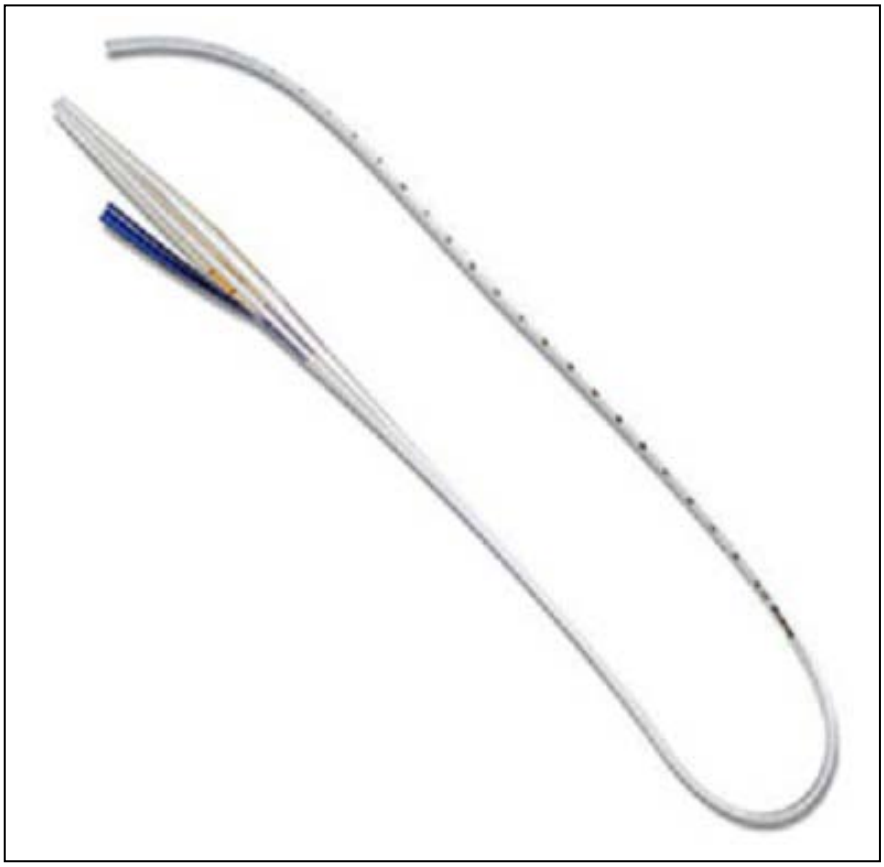


Figure 4: Double lumen Replogle suction tube (Adapted from Covidien online brochure http://www.covidien.com/criticalcare/pageBuilder.aspx?contentID=150958&webPageID=0&topicID=146881&breadcrumbs=0:121623,144286:0)

2.8 ASSOCIATED ANOMALIES

Anomalies associated with EA and TEF are mainly linked to the VACTERL complex. VACTERL refers to the anomalies of the vertebrae or spinal columns (V), atretic gut (A), cardiac anomalies (C), tracheoesophageal defect (TE), renal agenesis (R) and limb defects (L). If 3 or more of this defects are detected, VACTERL association is present and this occurs in 25% of babies with EA and TEF (Smith 2006). The most common anomalies recorded in previous studies were cardiac defects, followed by vertebrae, renal, atretic gut and limbs. Rate of mortality among babies of EA and TEF with cardiac anomalies are significantly higher than those without (Encinas et al. 2006).

It is believed there is a keystone changes in the early embryogenesis that leads to the wide spectrum of anomalies in a very consistent manner. The Shh gene is known to play an important role in EA. The Shh gene encodes an intracellular signalling molecule and its deficient will produce VACTERL anomalies in mice. Some studies have also shown that overactivity of the Shh gene can lead to branching of the fistulous tract from the lung and lead to TEF. It is also shown that Shh gene plays an important role in the development of the hindgut. The defect in this gene will lead to hindgut anomalies like imperforate anus that is commonly seen in cases of EA (Smith 2006).

Another gene, the DLL gene was recently discovered having missense mutation in a patient with VACTERL complex. Although the relationship between the DLL and Shh gene is unclear, it is unlikely the act in a separate pathway in causing the VACTERL complex.

Vertebral anomaly occurs in about 24% of babies with EA (Keckler et al. 2007). Vertebral defect is usually associated with other lesions of the axial spine including the ribs. The most common combination of anomalies consisted of rib anomalies, vertebral body defects, and tethered cord. Vertebral anomalies did not contribute to mortality (Keckler et al. 2007). In a review of 40 patients, an increased mortality was seen in patients with an extra thoracic vertebral segment. This observation was associated with an increased anastomotic leak rate, theoretically due to greater tension as others have found a wider gap due to a higher proximal pouch in patients with an associated anomaly of the axial skeleton (Upadhyaya et al. 2007).

Anorectal malformation was noted to occur with the incidence of 14.3% (Keckler et al. 2007). The defects associated with VACTERL malformations are higher in this group of patients. Detecting anorectal malformation will indicate to the physician to look hard for other associated anomalies. The following probability for the displaying one of the other VACTERL defects are vertebral(58.3%), duodenal atresia (16.7%), cardiac (58.3%), internal urinary (58.3%), limb (33.3%), and chromosomal (8.3%) (Sinha et al. 2008).

Cardiac anomalies are detected in 32.1% of the patients with EA. The most common component of heart disease was a ventricular septal defect occurring in 22.3%, which was a component of multiple heart lesions in most patients as an isolated ventricular septal defect occurred in only 7.1% (Encinas et al. 2006). Notably, cyanotic heart disease was found to be uncommon with 4.5% patients presenting with such a defect, and all were tetralogy of Fallot. Of the population of patients that has a tetralogy of Fallot, a worse outcome has been recognized for those who have extracardiac manifestations (Encinas et al. 2006).

Encinas et al. reported a 50% mortality for patients that have a tetralogy of Fallot and another manifestation of the VACTERL complex.

Urinary malformation occurs in about 17.0% cases (Keckler et al. 2007). Vesico-ureteral reflux was the most common anomaly. Other types of urogenital anomaly are renal agenesis, horseshoe kidney, polycystic kidney and cloacal anomaly (Uehling et al. 1983). In EA patients with urinary anomaly, other VACTERL defects that present concomitantly are vertebral (47.4%), anorectal (36.8%), cardiac (73.7%), limb (26.3%) (Keckler et al. 2007).

Skeletal malformation occurs in about 16.1% of cases. Peripheral skeletal anomalies were less common at 8.9% (Okada et al. 1997). Digital anomalies were the most common within this class, followed by an absent radius (Deurloo et al. 2004).

Other anomalies that overlap with VACTERL association are CHARGE syndrome, Trisomy 13, 21, 18 and Fanconi syndrome.

CHARGE syndrome is an autosomal dominant genetic disorder typically caused by mutations in the chromodomain helicase DNA-binding protein-7 (*CHD7*) gene (Vissers L.E et al. 2004). The acronym "CHARGE" denotes the nonrandom association of coloboma, heart anomalies, choanal atresia, retardation of growth and development, and genital and ear anomalies, which are frequently present in various combinations and to varying degrees in individuals with CHARGE syndrome. No single feature is universally present or sufficient for the clinical diagnosis of CHARGE syndrome, and numerous

guidelines have been published to aid in establishing a likely clinical diagnosis (Pagon R.A et al. 1981).

Blake et al suggested that a typical clinical diagnosis of CHARGE syndrome requires the presence of at least 4 major features or 3 major features plus at least 3 minor features. Major features include ocular coloboma or microphthalmia, choanal atresia or stenosis, cranial nerve abnormalities, and characteristic auditory and/or auricular anomalies. Minor features include distinctive facial dysmorphology, facial clefting, tracheoesophageal fistula, congenital heart defects, genitourinary anomalies, developmental delay, and short stature (Blake et al. 1998). Other frequently associated abnormal findings include characteristic hand dysmorphology, hypotonia, deafness, and dysphagia (Verloes A 2005).

A developmental defect involving the midline structures of the body occurs, specifically affecting the craniofacial structures. This defect is attributed to arrest in embryologic differentiation in the second month of gestation, when the affected organs are in the formative stages (choanae at 35-38 days' gestation, eye at 5 weeks' gestation, cardiac septum at 32-38 days' gestation, cochlea at 36 days' gestation, external ear at 6 weeks' gestation) (Jones K.L 1997). The prechordal mesoderm is necessary for the development of the mid face and exerts an inductive role on the subsequent development of the prosencephalon, the forepart of the brain.

The mechanisms suggested are:

(1) Deficiency in migration of cervical neural crest cells into the derivatives of the pharyngeal pouches and arches.

(2) Deficiency of mesoderm formation

(3) Defective interaction between neural crest cells and mesoderm, resulting in defects of blastogenesis and hence the typical phenotype.

CHARGE syndrome and EA/TEF are related via the overlap in the VACTERL association. Both these syndromes can be confused on presentation as they exhibit common features such as tracheoesophageal fistula, cardiac malformations and genitourinary anomaly. Although the management of TEF do not differ, it is important to identify the right syndrome the baby is affected with to identify all the other associated defects and treat them accordingly.