Acquired Aero Digestive Fistula in Adults- Case Series and Review

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Abstract

An acquired tracheoesophageal fistula portends a devastating prognosis complicated by recurrent pulmonary infections and malnutrition. Recently, prolonged intubation has emerged as the leading benign etiology, whereas malignant causes may be related to direct involvement of cancer or as a response to therapies including anti-angiogenic drugs. Management options include surgery and utilization of endo-prosthetic implants. There has also been a paradigm shift towards consideration of quality of life apart from mere survival in selection of treatment options. Most of our existing source of knowledge precedes some of these new developments. Herein, we present illustrative cases of aero digestive fistulas that portray both traditional and emerging etiologies. As much of our knowledge comes from the surgical literature, we review the literature to orient ourselves to tracheoesophageal fistula management from a non-surgeon's perspective. We hope this will help in early suspicion, diagnosis and prompt intervention in relevant clinical context.

Keywords: Tracheoesophageal Fistula (TEF); Tracheostomy Tube; Endotracheal Tube

Introduction

Acquired tracheoesophageal fistula (TEF) in adults, though uncommon, is a clinical entity that entails grave nutritional and pulmonary complications. Therefore a thorough understanding of its etiology, diagnosis and management helps in early detection, improvement in quality of life, and prolongation of meaningful survival in affected individuals.

The common etiologies of acquired TEF, both malignant and nonmalignant, have seen a shift in spectrum over the years, transitioning from an underlying disease process and trauma to the sequelae of modern therapeutic endeavors. Prolonged compression from an inflated endotracheal or tracheostomy tube cuff, coupled with nasogastric tube has emerged as the commonest cause of acquired nonmalignant tracheoesophageal fistula. Likewise, fistulas developing from the effect of radiation therapy, and certain chemotherapeutic regimens have increasingly been reported in the malignant disease population.

Even though specific etiologic variants of aero digestive fistula have been reported in detail in recent years, a comprehensive review of adult acquired TEF has been lacking among existing literature apart from articles focusing on surgical and non-surgical management. We describe several cases from our experience to portray some commonly observed presentations of TEF in present day practice. An awareness of the same will help identify similar scenarios within the early window of opportunity to guide appropriate management.

All 4 cases were diagnosed and managed in an urban University center in United States with availability of multispecialty expertise over a period of two years. As patients in all of these cases were not alive to provide consent for reporting, confidentiality was preserved while reporting individual health information. Approval was obtained from hospital institutional review board for retrospective report of case series with due diligence to preserve patient confidentiality and anonymity.

Case Series

Case 1

A 74 year old African American female with a history of diabetes, dyslipidemia, hypertension and obstructive sleep apnea was admitted with worsening shortness of breath attributed to exacerbation of congestive heart failure. Her course was complicated including a right adrenalectomy for an incidentally discovered mass with a postoperative course complicated by retroperitoneal bleeding, exploratory laparotomy, and phrenic artery embolization. She was intubated and mechanically ventilated for 18 days when tracheostomy placement was performed for persistent respiratory failure and failure to wean from mechanical ventilation. After 45 days, the patient was discharged with a size 6 cuffed tracheostomy tube. Two weeks after discharge, the patient was readmitted with progressive dyspnea, cough, and sputum production. An esophagogram demonstrated a high cervical tracheoesophageal fistula with passage of dye into the respiratory tract. A bronchoscopy and esophagoscopy was performed subsequently, which confirmed a patent tracheoesophageal fistula in the posterolateral wall of trachea, 2.5 cm from tracheal stoma. There was also an evidence of 60% circumferential tracheal stenosis, with inflammation along the posterior wall. Multiple biopsies were obtained from both the tracheal and esophageal aspects of the fistula which were negative for malignancy. The patient was supported with parenteral nutrition and surgical repair was offered. As the patient declined surgery, an endoscopic approach was chosen. A covered self expanding Ultraflex™ stent was placed in the esophagus with confirmed closure of the fistula on follow up esophagogram. After clearance by swallow evaluation, the patient was restarted on oral nutrition and was discharged to a rehabilitation facility.

Case 2

A 68 year old Caucasian female was admitted from home with complaints of coughing up of yellow fluid with particles from her tracheostomy port. Symptoms increased progressively leading to shortness of breath at rest over a 5 day period. The patient's tracheostomy (size 6 cuffless Shiley™) was placed after modified radical neck dissection for papillary thyroid carcinoma 4 years antecedent. The procedure was complicated by iatrogenic paralysis of bilateral vocal cords. In the interval between initial surgery and presentation, the patient had been treated surgically for recurrence of malignancy in her left parotid gland. Moreover, 4 months before presentation, she was found to have a left lower lobe adenocarcinoma excised through wedge resection although lymphovascular and visceral pleural invasion was present at the time of surgery. She was treated with Pamitrexed and Bevacizumab. Upper endoscopy and bronchoscopy was performed and a 7.5 mm fistula was found in the left posterolateral junction of membranous and cartilaginous trachea just below the tip of the tracheostomy tube, and 7.8 cm above the vocal cord. The fistula was 19 cm from gums on the esophageal aspect and had a small ulceration proximal to it with benign tissue histology. There was associated ballooning of inner mucosal layer of the esophagus with necrotic tissue and scarring above the carina. Biopsy obtained from the necrotic area was positive for adenocarcinoma. On confirmation of malignancy, endoscopic stent implantation was chosen for management. A 16 x 60 mm Aero™ stent was first inserted in the trachea, followed by a 10 x 18 mm covered Wallstent™ in the esophagus. Unfortunately, the patient persistently failed swallowing evaluations with recurrent aspirations. One such aspiration event resulted in pneumonia complicated by sepsis, and subsequently, the patient opted to pursue palliative care.

Case 3

A 62 year old Caucasian gentleman was admitted with complaints of difficulty swallowing and a 50 pound weight loss over 1 month. Dysphagia was for both solids and liquids and was not associated with cough, shortness of breath, fever or chills. An esophagoscopy done on admission showed a friable mass in distal 3rd of esophagus with near total luminal obstruction. Biopsy came back positive for poorly differentiated adenocarcinoma and staging studies showed evidence of metastasis to right pelvis and spine. A J tube was promptly inserted, and a 12 cm long partially covered wallstents was placed to bypass the luminal obstruction. Follow up esophagogram showed precise positioning of stent with no evidence of leakage to surrounding tissues. He was started on palliative radiation and chemotherapy with 5 Fluorouracil. 5 days after the placement of stent, patient started having high grade temperature with new onset shortness of breath. Chest X-ray revealed a new right lower lobe infiltrate with associated effusion, for which he was started on broad spectrum antibiotics coverage. The very next day, he had an acute episode of desaturation, hypotension, and septic physiology, for which he was intubated and started on pressors. The right lower lobe effusion was found to be worse, and chest X-ray appeared to show extra luminal extension of the esophageal stent. Pleural fluid analysis obtained by tube Thoracotomy showed evidence of empyema with polymicrobial flora. Repeat esophagoscopy

showed evidence of erosion through the esophageal wall with partial dislodgement of stent and erosion into both layers of right pleura and right upper lobe bronchus. Patient continued to deteriorate in spite of aggressive infection control measures and passed away on the 3rd day of intensive care unit admission.

Case 4

65 year old Caucasian female was admitted with complaints of persistent shortness of breath and painful swallowing of solid food for 3 months. She had an associated 15 pound weight loss and episodes of mild hemoptysis 3 to 4 times a day for 2 weeks before arrival. She had a significant history of COPD, and asthma for 10 years, for which she used Advair, Spiriva and albuterol. She also had a hiatal hernia treated by Niessen's fundoplication and had a right sided vocal cord paralysis, with 4 prior unsuccessful surgeries, the last one being 2 months before arrival. She was treated initially for acute exacerbation of COPD and also started on Unasyn for a left lower lobe infiltrate in chest X-ray. Due to persistent cough with any food intake, she had an ENT evaluation. Laryngoscopy showed vocal fold scar with marked sensory abnormality with complete anesthesia of left hemi larynx and marked hypoesthesia of the left. A subsequent barium swallow came back positive for aspiration with pharyngeal dysphagia. Oral diet was stopped and tube feeding was started. As she continued to have persistent secretion and cough with shortness of breath, a CT chest was ordered. The images showed a likely communication between esophagus and left main bronchus, with a left lower lobe infiltrate.

A subsequent esophagogastroduodenoscopy showed abnormal esophagus up to 25 cm followed by a stricture which was balloon dilated Few friable ulcers and chronic gastritis were seen around the gastro esophageal junction, but no definite fistula was visualized. The biopsies came back negative for malignancy. However a bronchoscopy done the very next day showed abnormal mucosa 20 cm from carina into left main stem bronchi, with a tracheobronchial fistula covered by a mucous flap. The area around the fistula was splayed by an enlarged left hilar lymph node, which on prior CT scan showed evidence of central necrosis. Biopsy from left lower lobe lesion came back positive for invasive adenocarcinoma of lung, and staging studies showed left hilar adenopathy with SUV uptake of 6.5. A repeat esophagoscopy was done and 10 x 18 mm covered Boston Scientific stent was deployed in the fistula area, with successful closure. The adenocarcinoma was staged as stage 3B, and she was started on chemo radiation. The tracheoesophageal fistula was attributed to erosion from metastatic hilar lymph node. She had a jejunostomy tube placed for nutritional support.
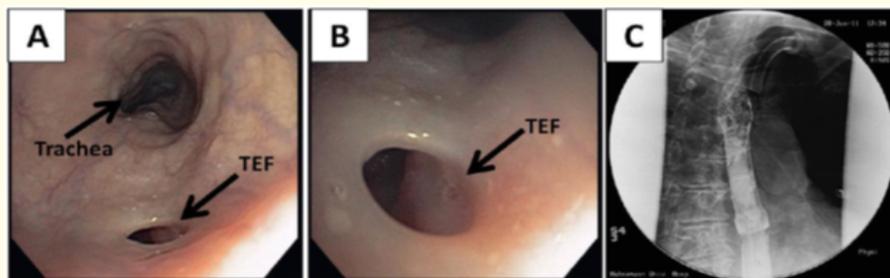

Figure 1: Bronchoscopic visualization of the airway from Case 1. A. Visualized fistula in the posterolateral wall of trachea. B. Close-up view of the fistulous tract with smooth contours. C. Flouroscopic image of the patient after placment of the esophageal stent.
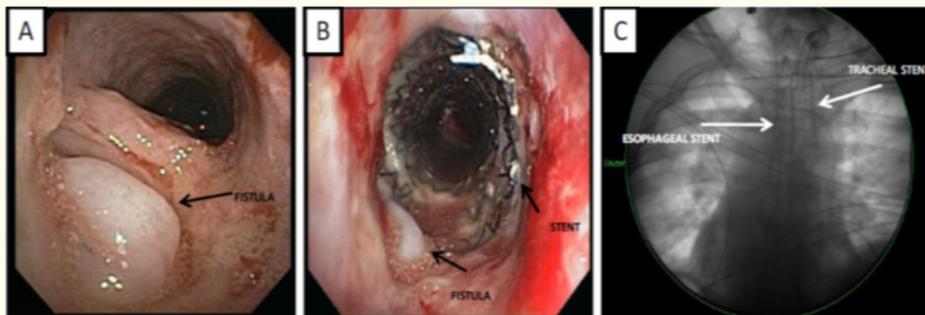

Figure 2: A: Visualization of the fistula from the tracheal aspect with out pouching of theesophageal mucosa through it. B: Same fistulous area after placement of the Aero stent. C: Fluoroscopicview of the esophageal and tracheal stent in situ.
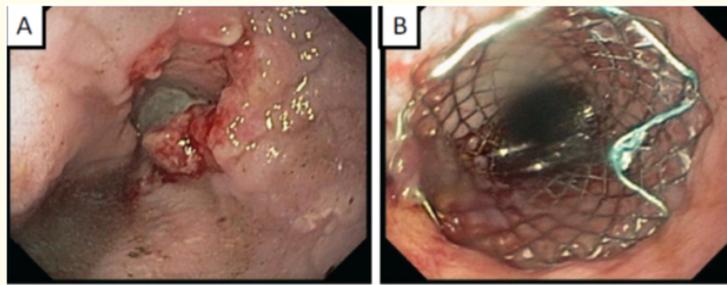
Figure 3: A: Esophageal luminal obstruction from tumor mass on endoscopy. B: Same patient after placement of esophageal stent.
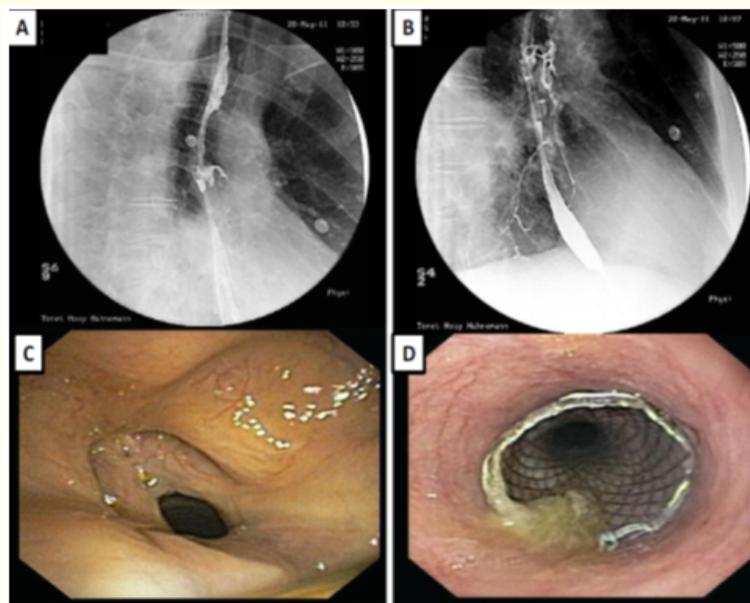

Figure 4: A and B - Fluoroscopic image of the leakage of dye from esophagus to airway.
C- Tracheal stenosis on bronchoscopy. D- Placement of esophageal stent.

Etiology and Pathogenesis

The etiopathogenesis of acquired tracheoesophageal fistulas can be broadly categorized into malignant and nonmalignant. Certain patient related risk factors act in aggravating the process, irrespective of the primary etiology (See table 1).

- Uncontrolled diabetes mellitus
- Steroid use
- Coexisting infections
- Hypotension with resultant tissue hypoperfusion
- Poor nutritional status
- Excessive motion of endotracheal tube in intubated patients.

Table 1: Risk factors for TEF.

Malignant TE Fistula

In one of the largest and most expansive review of malignant TEF, Burt and colleagues described their findings on a series of 207 patients admitted to Memorial Sloan Kettering Cancer center (MSKCC) between 1926 to 1988 [11]. The age range of the affected patients was from 21 to 90 years with a median of 59. The primary tumor site reported in this study, showed a clear predominance of esophageal (161 - 77%) and bronchogenic cancers (33-16%), a finding subsequently corroborated by numerous other studies. Other less common causes included trachea (5 - 2%), metastatic mediastinal lymph node and Hodgkin's disease (5 - 2%), larynx (3 - 2%) and thyroid [1]. The risk of developing fistula was also significantly higher in esophageal cancers (4.5%) compared to primary lung malignancy (0.3%). In the largest study to date of malignant tracheoesophageal and bronchoesophageal fistulae, Martini and colleagues confirmed this observation, with a reported incidence of 4.94% in 1943 esophageal carcinoma patients, and 0.16% among 5714 lung cancer patients [7]. He also reported a 14.75% incidence of fistulas among the 41 tracheal malignancy patients. In some recent studies, incidence of fistulization has been reported to be as high as 10% in esophageal malignancy patients. The respiratory location of the fistula involved trachea in 110 (53%) patients, followed by Left main bronchus (22%), right bronchus (16%), lung parenchyma (6%), and multiple sites in 2%, thus justifying the term esophagorespiratory fistulas or further broadly aero digestive fistulas.

The pathogenesis of malignant esophagorespiratory fistulas has historically been attributed to direct tumor invasion, tissue necrosis and erosion of tissue barrier between esophagus and airway at varied levels. Cancer primarily arising in either membranous tracheal wall can invade into the esophagus and vice versa, with the adjacent areolar tissue providing microenvironment for tumor growth. In addition a large esophageal tumor mass can mechanically impinge on the thin membranous tracheal wall which is only 4 mm in average thickness. With time this leads to ulceration ad necrosis and eventual fistula formation in a devitalized tissue.

However Burt., *et al*. in their report observed that most malignant TEF presented after prior treatment of the primary cancer with a median time from treatment with chemo radiation to appearance of TEF being 347 days [11,28]. On similar vein, Daffner and associates also reported that among individuals at high risk of developing tracheoesophageal fistula, based on evidence of retro tracheal abnormalities in chest radiograph, more than 60% progressed to fistulization during palliative therapy with chemoradiation [46]. These observations shift the pathological focus from direct tumor invasion to a final common pathway of local disease, devascularization from therapy, and resultant progressive tissue erosion. More importantly they allude to the fact that therapeutic measures such as chemotherapy, surgery and instrumentation, radiation, laser treatment, and rarely pressure necrosis from a prior placed stent have a telling role in the evolution of hitherto labeled malignant tracheoesophageal/bronchoesophageal fistulas.

Martini., *et al*. [7] showed a 73.9% incidence of malignant tracheoesophageal fistula post radiation compared to 26.1% incidence pre-radiation in their report on 111 cases. Chemotherapy alone in the setting of cancer involving full thickness of trachea and esophagus, has been reported to have a 6% rate of tracheoesophageal fistula while radiation has a risk of 73.9%.

Relevant to our case 3, recent literatures have also reported an increasing incidence of aero digestive fistula in patients on multimodality treatments involving ant angiogenesis agents Bevacizumab with chemoradiation for colorectal carcinoma, head and neck and lung cancers [6,9,40]. Ever since their advent in 2007, Bevacizumab has been hailed as a vital addition to the existing chemoradiation, thus improving survival in non-small cell lung cancer and advanced colorectal cancer, and improving progression free survival in breast and renal cell cancer [40].

However in 2009, Spiegel and coworkers published a report of two sequential single arm phase 2 trials of Bevacizumab added to conventional chemotherapy in stage 2 Small cell lung cancer and stage 3 non-squamous non-small cell lung cancer (SCLC) [9]. 2 among 29 patients in the SCLC arm developed TEF within a year, while 2 among 5 patients in the Non-small cell lung cancer arm developed fistula within 6 months. In addition 1 patient developed fatal aero digestive hemorrhage, likely from fistulous erosion of innominate vessel, 4 months into maintenance therapy. The authors reported an additional incidence in a previous study on same multimodality regimen. Both studies were closed early to enrolment. All 5 of these patients were found to have grade 3 esophagitis during chemoradiation and Bevacizumab induction, though none of the other agents involved in the regimen had been associated with fistula in prior published phase 2 trials. It is hypothesized that antecedent mucosal injury from combined modality treatment, followed by impaired neovascularization and wound healing with Bevacizumab accounted for this effect [6].

Collectively these observations suggest that additional studies of these novel antiangiogenic agents in combination with chemoradiation are necessary to obtain their long term effects on tissue integrity. Also in a patient evoking clinical suspicion of aero digestive fistula, prompt identification of Bevacizumab as a potential cause and further decision on its continuation becomes a clinical priority.

Nonmalignant TEF

Benign tracheoesophageal fistula accounts for about 50% of acquired aero digestive fistula in adults. Before the 1960s, the most frequent etiology was direct and indirect trauma, and granulomatous infection. In a recent case series from Mayo clinic, Shen and colleagues reported esophageal surgery (31.4%) and trauma (17.1%) as the commonest etiologies of fistula in their registry of 35 cases from 1978 to 2007 [1]. This specific variant of TEF has a higher incidence of distal tracheal and bronchoesophageal fistula. Traumatic aero digestive fistula typically develops 3 to 10 days after a blunt chest trauma. The pathogenesis involves compression of trachea and esophagus between sternum and the vertebral bodies with occasional laceration of the membranous trachea. There is subsequent necrosis from progressive impairment of blood flow. Immediate fistulization could also occur with simultaneous rupture of both trachea and esophagus. Hause and colleagues reported a 3.9% incidence of TEF after performing 785 esophagectomies [38]. The direst surgical causes among them involved surgical injury or ischemia after extensive peritracheal dissection.

However review of contemporary literature almost ubiquitously confirms that the most frequent cause of acquired nonmalignant tracheoesophageal fistula is the prolonged presence of a cuffed endotracheal or tracheostomy tube. Apart from known risk factors for evolution, the biggest threat to this group is sustained over inflation of the cuff, and excessive motion of the tube. Though Flege was the first to report tracheoesophageal fistula caused by cuff related injury in 1967 [20], it was Thomas who in 1973 first reported a large series of 46 patients, with fistula caused by cuffed tubes [47]. The pathological basis was first described by Cooper and Grillo in 1969 [3,29] and earlier by Pearson, Goldbarg and Da silva in 1968. They studied tracheal specimens, en bloc with cuffed tracheostomy and endotracheal tubes from autopsy of patients who had received prolonged assistance from cuffed tubes. In the process they were successfully able to demonstrate a universal evidence of circumferential tracheal tissue injury from pressure necrosis limited to the area around the cuff.

Starting 48 hours after insertion, evidence of superficial tracheitis with fibrin deposits was seen around the cuff site, and often extending up to carina. Subsequently small shallow ulcerations appeared overlying the anterior portions of the cartilaginous rings, the six and extent of which increased with time, leading finally, to the exposure of the cartilage. At about 10 to 14 days, there is softening, splitting, and fragmentation of the cartilage, with segments of the cartilage totally missing. The tracheal wall in the process loses any firm support and bulges at an area extending from 1.5 cm below the margin of the tracheal stoma to up to 2.5 cm further down. Damage to the compliant membranous portion was also seen, though less often than the cartilaginous portion. On continued exposure to high cuff pressure, and in presence of a rigid nasogastric tube in the esophagus, the intervening tissue devitalizes faster. Thus full thickness erosion develops through the trachea to produce a fistula, to the esophagus posteriorly and to the innominate artery anteriorly [29].

Role of associated infection or even the colonizing bacterial flora in tissue disintegration have also been debated. Additional noncircumferential injuries were also seen at the tip of the tracheostomy tube, and apart from fistulization, significant tracheal stenosis, lateral instability at the stomal site and tracheomalacia were also seen. The introduction of high volume low pressure cuffs ever since, has reduced the incidence of TE fistulae, yet prolonged intubation remains the leading culprit among non-malignant etiologies. Malnutrition, respiratory sepsis, poor blood glucose control, concomitant use of steroids can all contribute to pathogenesis as well [4].

Nonmalignant tracheoesophageal fistula has also been reported with granulomatous infections, particularly with Mycobacterium tuberculosis and histoplasma infections. Temes and associates reported 3 cases in patients with AIDS, a population well known to have predisposing esophagitis, and underlying malnutrition [43]. Table 2 sums up the reported etiologies of nonmalignant aero digestive fistulas. Table 2 gives a comprehensive list of potential etiologies of benign TEF.

- Prolonged mechanical ventilation.
- Esophageal surgery.
- Laryngotracheal trauma.
- Granulomatous disease.
- Airway stent erosion.
- Complication of radiation.
- Caustic lye ingestion.
- Recurrent fistula as a complication of Crohns disease.
- Complication of endoscopic antireflux procedures.
- HIV/AIDS.

Table 2: *Benign etiologies of TEF.*

Clinical features

The first clinical sign of a newly developed aero digestive fistula is a sudden increase in tracheal secretions.

Most benign fistulas are diagnosed while patient is still on mechanical ventilation. Certain clinical signs should trigger an alarm in the mind of the astute clinician. That includes aspiration of liquids or gastric contents from tracheobronchial tree, a progressive abdominal dilatation under positive pressure ventilation, and an unexplained discrepancy between inhaled and exhaled tidal volumes in ventilator. The patient if continues to remain undiagnosed, subsequently develop recurrent pneumonia with polymicrobial flora, and rarely have hemoptysis spells. Macchiarini., *et al.* in their case series of 32 patients reported 73% patients with at least 3 of the following - a) ≥ 15% weight loss b) severe hypoproteinemia c) Persistent dyselectrolytemia d) Acute kidney injury e) cardio respiratory failure or coma [4]. All of their patients also had septic syndrome with 53% having MRSA in their sputum.

Malignant tracheoesophageal fistula on the other end has a far more grave presentation, with a reported median survival time of 1 to 6 weeks, if left untreated. "Ono's sign" i.e. cough spells with swallowing efforts, with liquids and particulate food matter in sputum is a salient clinical finding. Patients also develop signs of chronic aspiration including cough, fever, halitosis, dysphagia, odynophagia, chest pain, and recurrent pneumonia. Burt and associates in their case series of 207 patients reported the following symptoms in order of incidence- Cough (56%), Aspiration (37%), fever (25%), dysphagia (19%), pneumonia (5%), hemoptysis (5%) and chest pain (5%) [8]. Balazs., *et al.* reported a 1.5% incidence of esophagopulmonary malignant fistula in their series of 264 patients [11]. Lung abscess was the most frequent and dreaded complication of this form of fistula. All of the patients had persistent infection and clinical deterioration in spite of airway stent placement. In fact Rodriguez and Jimenez points out that in this particular form of aerodigestive fistula, stent placement actually worsen the problem by impairing natural drainage of the abscess [6].

Diagnosis

An awareness of the appropriate clinical setting to the evolution of TE fistula is vital to early detection. In traumatic setting, one should always scrutinize for obvious evidence of chest trauma including subcutaneous air, pneumothorax, pneumomediastinum, rib fracture, or hemoptysis.

Suggestive clinical signs and symptoms warrants further diagnostic work up. On routine chest X-ray the cuff of the endotracheal tube may be seen outside the tracheal lumen. Esophageal dilatation with air distal to the fistula site, though subtle, is a pathognomonic finding. A CT scan may show defect between the trachea and bronchus. In patients having the ability to ambulate and swallow, a water soluble Omnipaque contrast study or a barium contrast study shows the fistula in 70% of case and identifies the site, dimension, and direction of the fistula. Endoscopic evaluation however remains the gold standard of diagnosis, and evaluation for subsequent management. A simultaneous Bronchoscopy, and esophagoscopy, often in the same setting is performed for localization of the fistula. Esophagoscopy can only visualize a large lesion or a neoplastic lesion, but may miss fistula hidden in necrotic tissues. In certain benign disease, a mucosal fold

may cover the esophageal orifice of the fistula and prevent instant identification. Hence Bronchoscopy is the preferred approach. After the bronchoscope is inserted into the airway, the tracheostomy cuff, if present is deflated, and the canula withdrawn, to visualize the involved mucosa circumferentially. With the bronchoscope in situ, an esophagoscope may then be inserted, and methylene blue or air instilled to observe for seepage of dye into the respiratory tract. The Bronchoscopic evaluation should precisely localize the fistula, defining its distance from the cords, carina and tracheostomy stoma. Multiple biopsy samples are obtained from the rim of both tracheal and esophageal aspect of the fistula, to rule out underlying malignancy. Finally thorough pulmonary toilet must be performed as an initial treatment to improve patient's respiratory status.

Benign aerodigestive fistula

Because of the need for appropriate patient selection, preoperative nutritional intervention, infection control and airway management, a multidisciplinary approach in a centralized equipped unit has been emphasized upon in literature, time and again.

When a patient is deemed to be a surgical candidate, a thorough assessment of the fistula and surrounding tissue as well as preoperative optimization of the patient becomes necessary. Preoperative feeding jejunostomy with venting gastrostomy tube placement protects the airway from soiling and maintains nutrition.

Aggressive respiratory optimization is favored including a necessity to wean the patient from mechanical ventilation, particularly where the etiology is related to prolonged intubation itself. Aggressive treatment of aspiration pneumonia with broad spectrum antibiotics ensuring anaerobic coverage is recommended.

Anesthetic induction also involves key strategies including placement of endotracheal tube balloon distal to fistula to avoid inadvertent damage during incision. In a distal location close to carina, this approach is not feasible. Single lung ventilation to isolate the affected bronchus may also be a necessary or preferred approach.

Surgical techniques can vary between 1) exploration and repair of fistula only, 2) exclusion and bypass of affected esophageal segment or 3) Resection of the fistula. If significant soiling and contamination has occurred already, a reconstruction is preferably delayed for a later procedure, due to the higher risk of anastomotic dehiscence.

Grillo, Moncure and Mcennany, in 1976, first recognized the fact that both the fistula and the diseased trachea require repair [3]. They introduced a single stage procedure with sequential tracheal and esophageal repair and a muscle pedicle interposition as reinforcement. This remains the basis of all repair techniques of nonmalignant TEF till date, though there is a wide diversity of opinion about the specific nature of repair, and the time of surgery, depending on the etiology of fistulization (See table 3).
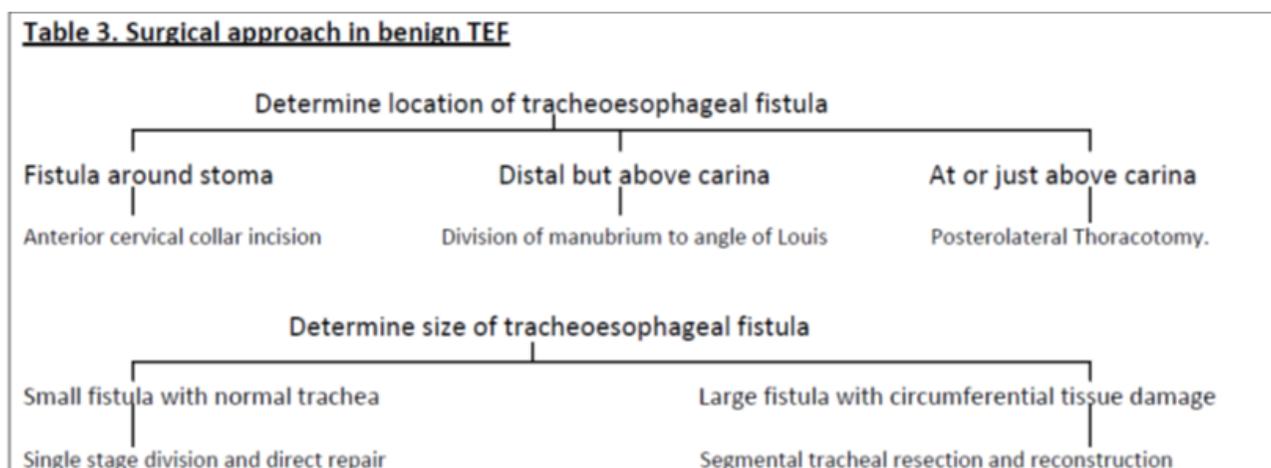

Table 3: *Surgical approach in benign TEF.*

Tracheoesophageal fistula from prolonged mechanical ventilation

As mentioned before, most acquired benign TE fistulas fall within this category. In view of the larger size of the fistula and the circumferential tissue injury, causing some degree of tracheal stenosis, a segmental resection and reconstruction of the trachea is the commonest surgical approach.

A resection anastomosis performed with continuation of postoperative positive pressure ventilation runs a high risk of anastomotic dehiscence and restenosis. Hence published studies on surgical repair of this subgroup of TEF have consistently advocated weaning the patient from ventilator, before pursuing a definitive single stage surgical repair [1,3,11,22,23]. Parallely an aggressive approach needs to be pursued to stabilize the patient and prevent fistula related complications. In the interim period two primary concerns are 1) an enormous risk of aspiration and pulmonary infection 2) poor nutrition which needs to be addressed meticulously. To prevent tracheobronchial soilage, a new tracheostomy tube, preferably distal extra-long type should be inserted and the cuff positioned carefully below the level of the fistula but above the carina. As Macchiarini points out, efforts should be made to avoid stenting or plugging of the defect with direct pressure of the endotracheal tube, cuff or stent, once primary surgical repair has been determined as the management strategy [4]. Placing esophageal stent results in enlargement of the fistula [49], while a tracheal stent causes inflammation and granulation tissue formation in an already stenosed tracheal mucosa.

Once satisfactorily weaned from the ventilator, adequate preparation is made for definitive surgical repair. A Bronchoscopy and esophagoscopy is performed by the operating surgeon to verify the location and size of the fistula, its relationship to the vocal cords, tracheostomy stoma and carina, and the extent of tracheal tissue injury, inflammation and circumferential stenosis. In separately published results on predominantly cuff related TEF, Mathisen., *et al.* Grillo, Moncure and McEnany advocated an anterior cervical collar incision involving the stoma, if the fistula is located within 2.5 cm of the stomal site [3,27]. For a distal fistula which is reasonable higher than carina, a division of manubrium to the angle of Louis is recommended, whereas a right Posterolateral Thoracotomy is preferred for a fistula at or just above carina. For a large fistula with circumferential tracheal damage, tracheal resection and reconstruction is recommended. After tracheal division, the esophageal defect is closed first in two layers over a nasogastric tube, and the tracheal anastomosis is performed subsequently. A pedicled strap muscle flap is mobilized and positioned over the esophageal repair to prevent recurrent fistulization. In the series by Mathisen and colleagues, 87.15 of the patients had fistula from the combined effects of airway tube cuff and NG tube. 76.3% of the patients were managed by tracheal resection anastomosis achieved through cervical collar incision in 2 out of 38 [3]. Thus it typifies the repair method for this predominant etiological subgroup.

In a fistula complicated by previous leak or radiation treatment, resulting contamination, inflammation and adhesions prevent a safe resection. Esophageal exclusion can be an alternate approach with access to the esophagus through a venting gastrostomy. It is thus isolated from both the proximal and distal end of fistula. A distal airway location of the fistula often necessitates this approach as it is challenging to achieve satisfactory airway decontamination, infection control and adequate pre and intra operative ventilation. Other recent reported techniques of repair include using a full thickness skin graft between trachea and esophagus [23].

TE fistula from surgical or traumatic etiology

Shen and colleagues in their report on 35 patients in Mayo clinic, Minnesota, mentioned that 51.4% of their patients were successfully treated with single stage diversion and direct suture repair of both the tracheal and esophageal defect without resection and anastomosis [1]. 57.1% of those surgeries were done by a right Posterolateral Thoracotomy. As an explanation they suggest that unlike the groups described by Mathisen, Hildenberg and Grillo, 48.5% of their patients had TE fistula from trauma or esophageal surgery. The resultant fistulas were smaller in size, were of distal tracheal or bronchial location, and were devoid of significant tracheal tissue damage. Such group of patients can thus be spared of resection and anastomosis and may still achieve equivalent outcome. Shen and colleagues also opined that in patients in whom segmental tracheal resection, and reconstruction is not required, ventilator dependence no longer remains an absolute contraindication. In 2000, Macchiarini and colleagues reported the outcome of different surgical techniques in their 20 year experience on treating post intubation tracheoesophageal fistula [4]. They summarily recommended tracheal resection and anastomosis with a muscle pedicle interposition in a single setting as a superior and safe approach even in small fistulas devoid of significant tracheal

injury. They justified their recommendations on ground of greater anterior and bilateral exposure of the area of damage, lesser risk of tracheal and esophageal devascularization, and lesser risk of recurrent laryngeal nerve injury. Furthermore with removal of the tracheal defect, and presence of an intervening muscle flap, membranous tracheal wall compression and stenosis becomes far less likely.

Resection is performed in large and recurrent fistulas. In proximal tracheal involvement, direct dissection of trachea is avoided after identification of fistula. The segment of esophagus attached to fistula is left in situ and the tracheal defect is closed with the overlying esophagus acting as a neomembrane. A gastric conduit is then utilized for reconstruction. In distal airway involvement, a thoracotomy followed by a segmentectomy or lobectomy is performed thus removing the fistula and affected distal airway. The esophageal defect, depending upon its size is either resected or repaired with an intercostal flap. Use of pericardial or pleural flap to buttress the repair site and prevent recurrence has also been reported.

Diversion of the esophagus with partial or total exclusion, in continuity with the fistula was also labeled as the most complicated, risky, and unsuccessful management strategy. Recommendations were made to avoid this procedure, unless measures of preoperative management in a ventilator dependent patient failed repeatedly.

Gudovsky., *et al.* reported a "conditionally radical" approach to surgically manage patients with tracheoesophageal fistula from caustic lye ingestion, which involves significant inflammation and scarring of esophagus ad periesophageal tissues [18]. It involved creation of an artificial esophagus with small or large bowel and thoracoplasty. Among other uncommon etiologies, TEF in patients with AIDS, in spite of being non-malignant, is considered unsuitable for surgical repair. Esophageal stenting is considered a reasonable palliative technique for such patients not amenable to surgical repair.

Management of malignant tracheoesophageal fistula

Malignant tracheoesophageal fistulas usually entail an ominous prognosis. Burt and colleagues in their series on patients treated at Memorial Sloane Kettering Cancer Center (MSKCC), reported a median survival of only 5 weeks [11]. Patient demographics, site and histology of primary cancer and site of fistula were not predictive of survival. However patients who received specific fistula directed intervention survived slightly longer than those undergoing supportive care. Equally important was the effect of immediate initiation of therapy once the patient was considered suitable. A therapy delayed by more than 1 week in a deserved candidate increased mortality almost exponentially. Balazcs., *et al.* in their report on 264 patients with tracheoesophageal fistula demonstrated presence of distant metastasis in 90.5% of patients at the time of diagnosis [8]. They had also received multiple treatment modalities, thus establishing tracheoesophageal fistula as a late event in the course of the disease. These patients can therefore be offered only palliative therapy directed at preventing tracheobronchial soilage and recurrent infections, relieving dysphagia and maintaining nutrition.

While encountering these patients and making appropriate treatment decisions, few relevant questions to ask includes:

- What is the stage of cancer and life expectancy?
- What are the goals of treatment?
- What are the patient's preferences for goals of care?
- What is the nutritional status and functional status of patient?
- Are anesthetic and treatment risks acceptable?
- Does the patient have a cardiopulmonary status to tolerate surgery?

The review of existing literature indicates that the functional status of patients, as well as physician expectations, based on underlying malignancy, determines the choice of therapy. Patients with disseminated malignancy and severe respiratory compromise are treated supportively with intravenous hydration, antibiotics, and hospice care. Whereas locally advanced disease with good performance status and minimal pulmonary compromise are offered choices of therapy. Treatment modalities can broadly be divided into endoprosthesis implantation, chemoradiation and surgery.

Endoprosthesis implantation

Esophageal stent placement has steadily emerged as the most successful and minimally invasive approach to seal the fistula, allow restricted swallowing, and avoid respiratory contamination.

Historically early techniques of esophageal intubation involved one of "traction", in which a laparotomy with gastrostomy was performed to anchor the orally introduced esophageal stent to the stomach and anterior abdominal fascia to prevent migration. The early stents were also of plastic or silastic material, and were fraught with procedure related problems. Their fixed external diameter necessitated aggressive dilatation of strictures thus causing acute perforations, while their fixed internal diameters limited their success in relieving dysphagia. They would also often cause central chest pain from the pressure from their thick walls.

In 1990s, self-expanding metallic stents (SEM) came as a welcome relief to the existing scenario. Knyrim., *et al.* in a study on 42 patients, demonstrated a significantly higher rate of complications, including perforations, and a longer length of hospital stay with plastic stents, in comparison to the metallic stents [44]. Ever since, metallic stents have been increasingly and extensively used in malignant TEFs. They are conveniently placed in fluoroscopy and endoscopy guided catheter based approach, using conscious sedation. The technique of deployment is "pulsion" as opposed to "traction". Pre-insertion dilatation of passage is necessary only if the stricture restricts the airway to 10 mm or less. Appropriate positioning of stent and successful closure of fistula should be verified within 24 hours of deployment by barium swallow and endoscopy. Though Burt., *et al.* reported a poor success rate with esophageal stents in the early days of their use, a subsequent summary of 24 published series since 1993, shows an effective and immediate closure of tracheoesophageal fistula in 89% of patients. The self-expanding metallic stents have also undergone a transition from uncovered to partially covered or completely covered stents.

Parallel stenting of the trachea and esophagus have been recommended in two clinical settings- 1) fistula in proximity to upper esophageal sphincter which may be inadequately closed by esophageal stent alone. And 2) high cervical TEF where an esophageal stent may lead to tracheal compression resulting in Dyspnea and airway compromise. If deemed necessary, airway stent placement should always precede esophageal stent.

Common complications involved with stent placement include stent migration, perforation, hemorrhage, airway sepsis, tumor overgrowth, food impaction, fistula neoformation, and stent fracture. In an interesting study, Kinsman., *et al.* reported a 36.4% incidence of life threatening complications in patients inserted with Gianturco Z stent with prior chemotherapy and radiation [48]. In comparison, only 2.5% developed similar complications in patients without prior therapy. The combined modality group also had a mortality of 23%, compared to 0% in the stent arm. Significant esophagitis, submucosal fibrosis, and ulceration associated with chemoradiation are speculated to be the contributing cause. Double stenting of airway and esophagus have also been associated with some unusual complications. Sporadic reports involve mediastinitis, mediastinal migration of prosthesis, pneumothorax, vascular fistula and an isolated report of superior venacaval occlusion.

A brief overview of each form of stent insertion is given below
Esophageal stent

Esophageal stents are most commonly Self expanding metallic stents (SEM) and are either 1) Partially covered or 2) Fully covered stents. The former has lower rate of migration but a higher rate of tumor ingrowth. The latter are more prone to migration distally.

A nitinol covered Ultraflex stent is preferred in airway fistulization by a malignant esophageal tumor. Its flared proximal and distal ends with flanges makes it less prone to migration and frequently achieves complete fistula sealing. If esophageal lumen is widely patent without any stricture, a large diameter silicone stent may be considered to minimize stent migration.

The most dreaded early complications include esophageal perforation or compromised airway resulting from tracheal compression. Tracheal compression can happen as a delayed complication as well. Other reported late complications include stent migration, bleeding, stent induced fistula and eventual tumor ingrowth.

Airway stent

Self-expanding metallic stents, both fully and partially covered, can be used in airway as well. In addition silicone stents and Dynamic stents have also been used. SEM are malleable to adapt to different airway size along with effective seal. Silicone stents in comparison, do not conform to airway anatomy. Because of variation in airway location of fistula, and the need for congruent shape of stent they can also be classified based on their shape as Straight, I shaped, L shaped or Y shaped stent. Y shaped stent or Dynamic airway stent are more suitable for a fistula in close proximity to carina.

It is somewhat uncommon to place airway stent alone unless there is obvious contraindication to esophageal stenting (unsuitable esophageal anatomy or prior complication from esophageal stent). In the reported retrospective data by Wang., *et al.* complete fistula closure was observed in 71.4% of patients (45/63) who had airway stent alone [22]. In a separate retrospective study reported by Chung., *et al*. there was a significant improvement in median survival in airway stent group compared to conservative management (69 vs 29 days) [10]. However Herth., *et al. i*n their evaluation of 112 patients with malignant ADF reported a significantly longer survival in esophageal and dual stent group compared to airway stent alone subset of patients. In addition recurrence rate was also higher in the latter. Initial fistula closer was 100% in all 3 subgroups.

Complications are more common with airway stents than esophageal stents. Early complications include initial chest pain, foreign body sensation, or cough to catastrophes of massive bleeding or respiratory failure requiring mechanical ventilation. Late complications can be minor symptoms of cough, chest discomfort, dysphagia or major complications like stent migration, bleeding, recurrent aspiration and airway compromise. Pressure necrosis and erosion contributes to most of the late complications. Recurrent fistula has been reported widely between 13 to 66% patients.

Double stent

Ke and colleagues in their evaluation of 62 patients with aero digestive fistulae reported a higher rate of fistula closure in double stenting group compared to airway or esophageal stent. The clinical benefit was equivalent in both silicone and metallic stents. However as reported by Huang., *et al.* that did not translate into a survival benefit in their outcome study of 50 patients [53].

The American College of Chest Physicians gives a grade 1B recommendation for double stenting or esophageal stenting only with SEMS for management of ADF. There are exceptions in which an airway stent can be considered along. They are

- Immediate concern for airway compromise
- Esophageal narrowing or obstruction that prevents the wire to be placed distally beyond obstruction
- ADF located in upper 3rd of esophagus
- Patients with adequate alternate source of nutrition like percutaneous gastrostomy tube.

Approach to placement

Esophagoscopy and bronchoscopy is performed together in the same setting. Initial evaluation is targeted at assessment for airway compromise which prompts the initial placement of an airway stent followed by an esophageal stent. Even if there is no obvious evidence of airway compromise, esophageal balloon insufflation mimicking the size of the stent should be carried out to ensure patent airway after placement of esophageal stent. Once an esophageal stent is placed, an esophagogram is performed in a few days to assess for persistent leak. If present, an airway stent should follow. In rare cases of refractory leak in spite of dual stenting, an Overlap stent may need to be placed in the same lumen - esophagus or trachea with overlap between the two stents.

An optimal stent length should cover at least 2 cm beyond the proximal and distal margin of the lesion with a diameter at least 10 - 20% larger than the internal lumen.

Alternative minimally invasive endoscopic approaches
Fibrin glue

Calcium and factor 8 added to fibrinogen and thrombin results in its conversion to fibrin mesh and may help in closure of small fistula in pediatric population. Their success rate is limited with risk of persistent leakage, abscess formation or inflow into the working channel causing endoscope damage.

When combined with Polyglycolic acid sheets (PGA) they have been reported to be more efficient in Esophago-pulmonary and Esophago-bronchial fistulae not amenable to airway stenting.

Septal button

Schmitz., *et al.* reported use of septal button to close a TE fistula post laryngectomy improving quality of life. They are originally used for closure of nasal septal perforation

over the scope clips

These devices are made of the metallic alloy nitinol and available in various sizes and depths. They are typically deployed at the esophageal or gastric aspect of the fistula using an applicator integrated to the tip of endoscope. One big limitation is the need for tissue suction and therefore somewhat soft and pliable fistula margin which is often absent with marginal fibrosis. They are particularly more effective in treating persistent leaks than primary repair of fistula, and can be used as a combined modality of treatment with stents and endoscopic sutures.

A recent variation is the Padlock clip (Aponos Medical, Kingston, NH, USA). Armellini reported a small case series in 2 patients with successful closure of fistula. It is aligned to the side of the endoscope and does not require the working channel [52].

Surgical approach

Direct closure and resection and reconstruction of the trachea, practiced in benign tracheoesophageal fistula is too heroic a measure for an incurable malignancy. Burt and associates, in their study reported a 30 day mortality of 60% with such surgical measures, and a zero survival beyond 6 weeks. Surgical modalities for palliation, therefore involves either esophageal exclusion or esophageal bypass.

Esophageal bypass

In this process, the section of the esophagus with the fistula is excluded by transecting the cervical esophagus and closing the distal end, followed by transaction of the distal esophagus and closure of the proximal end. Subsequently a gastric, colonic, or jejuna bypass is performed to the proximal esophagus.

Esophageal exclusion

In patients unable to tolerate bypass due to recurrent pneumonia, an esophageal exclusion is performed by exploring the neck, stapling the distal esophagus, and creating a cervical esophagostomy with the proximal end, for drainage of respiratory contents. The gastro esophageal junction is then stapled and transected, and a gastrostomy is performed for feeding purposes. It is the least tolerated of all palliation measures, due to frequent leakage of the esophagostomy and inability to have oral nutrition. Survival rates are also not improved with this option.

Chemoradiation

Though chemotherapy alone is not recommended for management of malignant tracheoesophageal fistula, there have been sparse but encouraging reports of radiation therapy as sole treatment modality. Burt., *et al.* reported a significant prolongation of survival with radiation compared to supportive care only. There are even 3 existing reports of healed malignant tracheoesophageal fistulas with radiation sessions alone.

Combined chemoradiation however has more encouraging results. Muto., *et al.* reported fistula closure in 17 out of 24 patients based on barium esophagography, though 3 subsequently redeveloped fistula [32]. Ahmed., *et al.* achieved closure in 4 out of 6 patients with aerodigestive fistula in the setting of esophageal carcinoma [33]. However the reappearance of fistula suggests that the transient closure may largely be an effect of soft tissue inflammation from radiation, thereby occluding the fistula.

With palliation and not survival duration, being the priority in treatment of tracheoesophageal fistula with advanced malignant disease, a more intense focus is necessary on the patient quality of life. In a comprehensive review of 35 patients with esophageal squamous cell carcinoma developing aero digestive fistula, Hu., *et al.* compared the effects of esophageal stenting, gastrostomy alone, and supportive therapy on the survival time, and patient related quality of life indices. The supportive therapy groups were maintained on parenteral nutrition and antibiotic therapy alone [14]. The stent group had lower scores in respiratory and feeding related symptoms in comparison to both supportive therapy and gastrostomy arm. However they had a survival advantage, and had significantly higher emotional and social functions. The gastrostomy group on the other hand, showed the least survival time, and a significantly low score in emotional function, and financial situation, compared to even basic supportive measures like fasting, antibiotics and intravenous nutrition. This indicates that in patients with malignant TEF, not amenable to stent insertion, gastrostomy should not be considered as a fallback option. Esophageal stent remarkably improved health related quality of life and should thus be considered a s a first choice in the treatment of malignant aerodigestive fistula.

Conclusions

Aero digestive fistula, a rare but potentially grave respiratory pathology is seen as a complication of varied benign and malignant disease etiologies. Prolonged mechanical ventilation with sustained cuff pressure from endotracheal and tracheostomy tube is the most common and clinically relevant benign etiology. Whereas advanced esophageal malignancy attributes to a major bulk of the malignant form. In view of its ominous pulmonary and nutritional consequences, awareness to the appropriate clinical setting for the evolution of TE fistula is necessary for early suspicion, prompt diagnosis, and immediate management measures.

A patient with nonmalignant fistula is ideally stabilized, weaned off the mechanical ventilation, and then treated with the goal of definitive single stage surgical repair, specifics of which varies with the cause, location and size of the fistula.

A malignant TE fistula on the other hand, has far more dismal prognosis and is treated preferably in a patient with modest functional status and less advanced stage of invasion. Contrary to benign disease, endoesophageal covered self expanding stents are considered the first line of therapy, with an airway stent or double stent as an additional requirement in special settings. Along with survival duration, health related quality of life should be a primary determinant of the choice of therapy in this subgroup of patients.

As newer knowledge emerges, we continue to become more aware of the merits of less invasive and better tolerated closure devices, and the hazards of otherwise novel anticancer agents like Bevacizumab as an etiology of TE fistula. More widespread population based research has become necessary in both spectrums, before such therapies are universally endorsed.

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