Endoscopic management of tracheoesophageal fistulas

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Abstract

Tracheoesophageal fistulas (TEF) are pathologic communications between the trachea and esophagus. TEF can lead to significant respiratory distress that may result in lethal respiratory compromise, often due to recurrent and intractable infections. Through the use of endoscopy, some TEF can be successfully repaired using different approaches depending on the size, location, availability, and experience of the treating endoscopist. The aim of this manuscript is to provide an up-to-date review of the endoscopic management of TEF for gastroenterologists.

Keywords Tracheoesophageal fistula, endoscopy, stents, over-the-scope-clips, tissue adhesives

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Introduction

Tracheoesophageal fistulas (TEF) are abnormal, pathologic communications between the posterior wall of the trachea and the anterior wall of the esophagus. TEF can be congenital or acquired, as well as benign or malignant. Most TEF in adults are acquired; congenital TEF are more commonly associated with esophageal atresia at birth. The majority of acquired TEF are due to esophageal and pulmonary malignancies. Other benign etiologies, such as caustic ingestion, prolonged esophageal intubation and surgical interventions, can lead to TEF formation [1-3].

TEF can be managed either surgically (open repair or thoracoscopic) or endoscopically, depending on their etiology, size, anatomy, and patient comorbidities [4]. Surgery is highly invasive and other options are typically investigated before this is undertaken. Endoscopic therapy has been shown to be a safe and effective approach in the management of TEF, with lower

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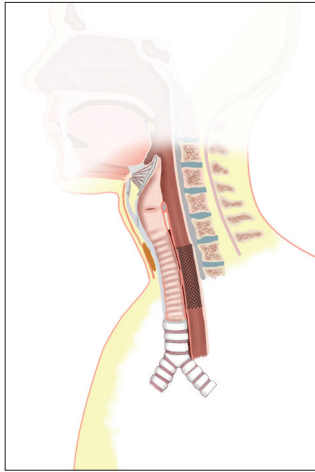
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morbidity and mortality compared to surgical interventions [5]. With rapid advances in therapeutic endoscopy, new techniques have emerged that can be used to successfully manage and repair TEF.

Endoscopic management

Esophageal stents

Esophageal stents are routinely used in an attempt to close and manage TEF [6]. Stents should be placed to cover the TEF as well as short sections of normal esophageal tissue both proximal and distal to the fistula. It must be stressed that esophageal stents do not provide an airtight seal over the TEF and aspiration can occur even in the setting of a perfectly placed esophageal stent (Fig. 1,2).

There are two basic types of stents available to endoscopists: self-expanding metal stents (SEMS) and silicone or plastic-based self-expanding stents; the latter have been largely abandoned in current practice and will not be discussed further. Self-expanding stents have the capacity to expand themselves more precisely into the lumen of the esophagus or trachea; they can theoretically fit most airway malformations [7]. Stents are available in two forms: partially covered and fully covered. Cover materials (such as silicone, polyurethane, and most commonly polytetrafluoroethylene) reduce reintervention rates, which range from 30-50% for uncovered stents, primarily because of complications from granulation tissue ingrowth [8]. To close a TEF, a covered or partially covered stent must be used.

SEMS have shown varying degrees of clinical success when used to treat TEF, ranging from 67-100% [9]. In a multi-technique, multicenter study of endoscopic TEF closure, Silon

Figure 1 Schematic diagram of tracheoesophageal fistula with an esophageal stent
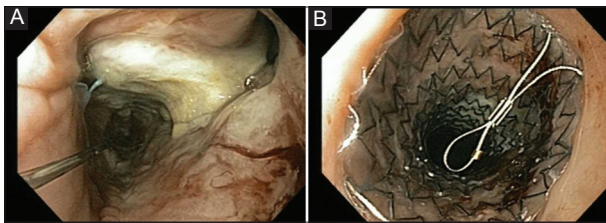
Figure 2 (A) Endoscopic image of a large tracheoesophageal fistula that developed following esophagectomy. (B) Same patient after placement of a self-expanding metal stent across the fistula

et al reported the use of SEMS in 92% of patients (n=25) and 85.7% of procedures (n=35). All were placed under general anesthesia and 88.9% were placed using fluoroscopic guidance. SEMS used as monotherapy showed a high technical success rate (n=13; 92.3%) and a relatively moderate clinical success rate (n=13; 53.8%). Five patients (38.5%) required additional procedures because of stent migration and aspiration (n=1), persistent fistula without aspiration (n=1), and aspiration with the stent remaining *in situ* (n=3). After five secondary interventions, clinical success was 80% (4/5). Secondary interventions included replacing esophageal stents, replacing an esophageal stent with over-the-scope clips (OTSC), and replacing with OTSC, a new esophageal stent, and an airway Y stent.

While esophageal SEMS are minimally invasive and are often associated with positive outcomes and improved quality of life, they are sometimes more effective when used in combination with other therapies, such as an airway Y stent or an OTSC [10]. The Y or bifurcation airway stent is typically used for conditions affecting the lower trachea, carina or the proximal bronchial lumen that may lead to airway obstruction or airway fistulation [11].

Combined therapy with tracheal and esophageal stents is useful and is indicated in the following instances: 1) esophageal stenting could compromise the respiratory tract via extrinsic compression; 2) if there is preexisting tracheal stenosis, in which case the airway stent should be deployed first; and 3) cases of

large fistulas (>20 mm) [7,10,12]. The study by Silon *et al* used tracheal stents in combination with esophageal stents as initial therapy in 6 patients. Esophageal stents were used for proximal fistulas while tracheal stents were used for proximal, middle, and distal fistulas. The technical success using this approach was 100%, while the clinical success rate remained low (33.3%), highlighting the difficulties in treating these lesions.

Adverse events associated with SEMS include migration following deployment, as well as symptoms of cough, dysphagia, nausea, gastroesophageal reflux, bleeding, perforation, pneumonia, tracheal compression and chest pain [6,7]. The frequency of chest pain after stent insertion has been estimated to be 5-50%, depending on how it is defined and studied [13]. Likewise, the frequency of stent migration can be as high as 40%, with the migration rate being higher with plastic or silicone stents [14,15].

Tissue adhesives: fibrin glue and cyanoacrylate

As an alternative to stents, endoscopists may revert to using sealants or tissue adhesives. The most commonly used sealants used in gastrointestinal endoscopy include cyanoacrylates, fibrin glues, and thrombin [16]. Cyanoacrylates are a class of sealants that solidify rapidly in the presence of a weak base, such as water or blood [17]. Fibrin glues are composed of highly purified, freeze-dried human fibrinogen with factor XIII in addition to a starter solution containing human thrombin. Upon mixing, the solution forms a clot that replicates the terminal phase of the clotting cascade [18]. Additionally, the use of commercial thrombin promotes the conversion of fibrinogen to fibrin [19]. This ultimately produces cross-linked fibrin polymers and a closed seal over the fistula.

Several case series have demonstrated successful outcomes following the use of cyanoacrylates for fistula repair; however, randomized control trials are lacking [20-22]. A systematic review compared the use of sealant with or without abrasion (23 articles and 57 pediatric patients) versus open surgery (21 articles and 108 patients) for managing recurrent TEF [4]. The study characterized the efficacy of each treatment via standardized comparison in 3 categories: single successful treatments, mean number of treatments performed, and treatment failures converted to an alternative procedure. In the endoscopic group, the sealant-only cohort (n=6) was found to be the most successful single treatment (n=4/6, 67%), having the least average number of treatments required (1.5) and treatment failures (n=1/6, 16.6%). However, it should be noted that the sealant-only cohort had a relatively small number of patients, which should be considered when interpreting the results.

There are other reports of relatively low success rates when sealant is used alone compared to higher rates in combination with other therapies [5]. Richter *et al* showed that sealant (fibrin with added aprotinin) combined with abrasion techniques had a higher success rate (n=15, 93.3%) compared to abrasion alone (n=8, 62.5%) and sealant alone (n=14, 78.6%) [23].

Gregory *et al* identified 11 studies involving 30 patients treated for recurrent TEF. The review found that combination therapy with fibrin glue and electrocautery was more effective

when compared to electrocautery alone: 86% and 67%, respectively [24]. Combination therapy was a safe alternative to open surgical repair, as only three patients experienced respiratory distress syndrome and one patient required a tracheostomy [24]. Other studies support and recommend the use of fibrin glue in combination with abrasive therapy as providing the best outcomes [25,26]. Additionally, societies such as the American Society for Gastrointestinal Endoscopy report that fibrin glue provides endoscopists with ease of use without any risk of damage to the endoscope [27].

Endoscopic clips

Endoscopic clips were originally designed to function as hemostatic devices, specifically in the gastrointestinal tract [28]. The through-the-scope clip system was the original iteration of endoscopic clips, but was limited by relatively small opening diameters and a sometimes suboptimal closure force [29,30]. The OTSC system was designed to overcome these limitations. Since then, several different clip shapes and sizes have been developed for use in different organs and different clinical contexts [8]. Other innovative clips, such as the Padlock Clip, have emerged and have been successfully utilized in the repair of TEF [31,32].

The technical overall success rate achieved by OTSC devices remains unclear. Haito-Chavez et al reported a large study involving 108 fistulas, 48 perforations, and 32 leaks. Of these, 16 cases involved esophageal fistulas, of which 6 resulted in technical failure [33]. It was hypothesized that the failure was due to fibrotic or retracted edges, which impeded an adequate opposition of defect borders. Additionally, using multivariate logistic regression, the study reported that the most important predictor of long-term success after OTSC closure was the type of defect, failure being reported most commonly in patients with fistulas. The study concluded that OTSC was more clinically successful in managing leaks and perforations.

In addition, we identified 10 case studies that specifically described the use of OTSC in the repair of TEF. All 10 cases were technically and clinically successful [31,32,34-40]. Almost all cases (9/10) used a single clip for primary (6/10) or secondary (4/10) intervention. Follow-up time ranged from 2 weeks to 8 months and only one case reported a complication of clip dislodgement (Table 1).

While information abounds on the use of OTSC in the repair of gastrointestinal leaks and perforations, data on the use of OTSC for repairing TEF remains sparse. As a result, the role of OTSC in the management of TEF remains unclear. Larger clinical studies are needed to evaluate its long-term clinical and technical efficacy compared to other endoscopic interventions.

Atrial septal defect (ASD) occluder devices

In cases where there is extensive fibrosis not amendable to the application of clips or adhesives, ASD occluder devices, namely the Amplatzer Occluder (Amplatzer Occluder; AGA

Table 1 Reports of over-the-scope clips used in the management of tracheoesophageal fistula

Study	Etiology	Number of clips	Fistula size and characteristics	Primary/secondary intervention	Initial clinical success	Initial technical success	Follow-up time	Complication
Armellini et al [31] 2015	Chemo-radiotherapy	1	Undefined	Secondary (unknown primary)	Yes	Yes	5 months	None
So et al [32] 2014	Chemotherapy	1	1 cm, epithelialized, densely fibrotic	Secondary (primary was fully covered stent)	Yes	Yes	Undefined	None
Zolotarevsky et al [34] 2012	Mediastinal infection	1	5 mm	Primary	Yes	Yes	1 month	Dislodgement
Vinnamala 2014	VATER syndrome	1	1 cm, epithelialized, densely fibrotic	Primary	Yes	Yes	Undefined	None
Ferreira et al [36] 2013	Post gastrectomy	1	4 mm	Primary	Yes	Yes	2 weeks	None
Shah et al [37] 2015	Post-intubation	1	1 cm, epithelialized, densely fibrotic	Secondary (primary was surgical stapling)	Yes	Yes	8 months	None
Rai et al [38] 2017	Post-ventilation	1	Undefined	Primary	Yes	Yes	6 months	None
Matsui et al [38] 2017	Esophageal cancer	1	Undefined	Primary	Yes	Yes	2 months	None
Rana et al [40] 2017	Tubercular infection	1	Undefined	Secondary (primary was multiple hemoclips)	Yes	Yes	6 weeks	None
Law et al [33] 2015	Radiation	Unknown	Undefined	Primary	Yes	Yes	Undefined	None

Medical Corp, Plymouth, MN), can be considered as an option to manage TEF. An ASD occluder device is a permanently implanted prosthetic that forms a mechanical barrier between the esophagus and trachea; it is supplied along with a catheter delivery system. The Amplatzer device consists of two polyester-coated nitinol discs connected via a thin waist and loaded into a catheter. The diameter of the discs typically ranges from 1-2 cm and can be matched to the size of the fistula. The discs are coated with polytetrafluoroethylene material, giving them a microporous surface that facilitates coverage by fibrous connective tissue and ultimately adapts to the patient's anatomy [41].

When the device is deployed, each ring expands on either side of the fistula, thus fixing it in place [42]. They can be used for temporary alleviation of a patient's symptoms while on mechanical ventilation, or for long-term management [43]. ASD occluder devices facilitate granulation after 1-6 months, allowing their effective usage in long-term management [44-46].

In 2010, Repici *et al* described the first use of TEF closure using an ASD occluder device in a 58-year-old male patient with a malignant recurrent TEF that occurred after intrathoracic anastomosis for an adenocarcinoma in the esophagus. This technique facilitated successful closure after unsuccessful endoscopic and surgical interventions. Fistula closure and granulation were confirmed at an 8-month follow up [47]. Cohen-Atsmoni *et al* described 2 patients with acquired TEF due to prolonged intubation, managed using this technique [43]. In total, only 6 successful cases have been reported of TEF closure using an ASD occluder device, demonstrating that this is largely an experimental technique in gastrointestinal endoscopy [44,47-51]. The most commonly reported complications associated with this technique are migration due to an incorrectly sized device, esophageal peristalsis, extrusion, or enlargement of the fistula [48,49]. No multi-patient studies have been reported and further studies are needed to fully evaluate the efficacy of this technique. Until the role of the ASD occluder is established in the management of TEF, it can be considered in extreme cases of TEF not amenable to other techniques.

Endoluminal vacuum-assisted closure (EVAC) therapy

EVAC is another technique which can potentially be used in the repair of TEF and other upper gastrointestinal defects [50,51]. EVAC creates a negative pressure environment while placing a polyurethane sponge in the lumen of the fistula. The sponge is connected via a nasogastric tube that continuously removes secretions and improves microcirculation. The process induces the accelerated formation of granulation tissue, which leads to closure of the lesion or fistula [52,53]. Though this technique has been used sparingly and reports are sparse, several case reports describe its use to successfully treat acquired TEF [54-58]. However, as with the ASD occluder device, large retrospective or prospective cohort studies are needed to establish its role in the management of TEF.

Concluding remarks

TEF can be congenital or acquired, as well as benign or malignant. Today there are a variety of endoscopic techniques that can be safely employed by endoscopists, surgeons, and respirologists to repair TEF. Clinicians may select an approach based upon the size of the fistula, location, availability and their experience. While some techniques are associated with minor adverse effects, these are rare. As of today, there are no official guidelines for repairing TEF, primarily because of the small number of cases reported [Q: Please check that this is the correct intended meaning] and the variable clinical success, which does not allow generalization. The endoscopic repair of TEF follows an underlying narrative throughout treatment strategies: combined approaches are more successful. Large head-to-head clinical studies are needed to compare and further extrapolate the long-term clinical and technical efficacy of these therapeutic strategies.

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