



AKADÉMIAI KIADÓ

Tracheoesophageal fistula due to *Candida* and *Actinomyces* co-infection: A case report and comprehensive review of the literature

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CASE STUDY



ABSTRACT

Acquired benign tracheoesophageal fistulas and bronchoesophageal fistulas (TEF) are typically associated with granulomatous mediastinal infections, 75% of which are iatrogenic. *Candida albicans* and *Actinomyces* are commonly occurring organisms, but are uncommon etiologies of TEF. Normal colonization and the slow growth characteristics of some species of these agents rarely result in infection, mycetoma, and broncholithiasis, and thus, delays in diagnosis and treatment are likely. Few reports describe *C. albicans* or *Actinomyces* spp. as the etiology of TEF or broncholithiasis. Herein, we report a case of benign acquired TEF secondary to coinfection of *Candida* and *Actinomyces* complicated by the formation of an actinomycetoma and broncholithiasis and a comprehensive literature review to highlight the unique nature of this presentation and offer a diagnostic algorithm for diagnosis and treatment of TEFs. Following a presentation of three months of productive cough, choking sensation, night sweats, and weight loss, a bronchoscopy revealed a fistulous connection between the esophagus and the posterior right middle lobe. Pathology identified a calcified fungus ball and a broncholith secondary to the co-infection of *Candida* and *Actinomyces*. This unique presentation of *Candida* and *Actinomyces* co-infection and the associated diagnostic algorithm are presented as education and a useful tool for clinicians.

KEYWORDS

bronchoesophageal fistula, *Candida albicans*, *Actinomyces*, co-infection, benign acquired TEF

INTRODUCTION

Tracheoesophageal fistulas and bronchoesophageal fistulas (TEF) may be congenital or acquired [1–3]; acquired TEF has been noted in advanced esophageal or respiratory malignancies [1, 2, 4], as a surgical complication, or as a result of traumatic or prolonged intubation [1–4]. Non-surgical causes include granulomatous etiologies, most notably tuberculosis, which has been the most common cause of benign acquired TEFs; however, iatrogenic causes make up 75% of all cases [2, 5–7]. *Candida albicans* and *Actinomyces* spp., when co-infecting, can form an actinomycetoma, which has not been previously reported as an etiology of benign acquired TEF [8, 9], or broncholithiasis, from erosion and extrusion of chronically inflamed or granulomatous tissue within the tracheobronchial tree [4, 5, 7]. Tuberculosis and histoplasmosis infections account for most cases of broncholith formation; few reports describe actinomycetoma as the etiology of broncholith and subsequent TEF formation. Herein, following institutional review board (IRB) approval, we present a case of a patient with a tracheoesophageal fistula secondary to an actinomycetoma that was further

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complicated by the formation of a broncholith, demonstrating an unusual complication of bronchopulmonary *Candida* and *Actinomyces* co-infection.

We also present a comprehensive literature review to better educate clinicians regarding this unique pathology's presentation, diagnosis, and treatment, other infectious causes of TEF, and known presentations of *Candida* and *Actinomyces* co-infection.

ETHICS

This report was approved by the Prisma Health IRB as non-human research; consent for publication was received from the patient.

CASE REPORT

A 77-year-old male with a medical history significant only for recurrent pneumonia and no other known chronic medical conditions presented to his primary care provider multiple

times over a year for complications related to recurrent aspiration, bronchitis, and dysphagia. He eventually presented to the emergency department (ED) with complaints of three months of productive cough, a sensation of choking, night sweats, and 5 kg of unintended weight loss. On exam, the patient was tachycardic and hypoxic, and a chest radiograph taken in the ED showed a consolidation in the patient's right middle and right lower lobe. The patient was treated with ceftriaxone and azithromycin and discharged home with ten-days of oral antibiotics; however, the patient continued to worsen and experienced increased dyspnea, which prompted a cat scan (CT) of the abdomen and pelvis that showed a focal calcified endobronchial lesion in the right mainstem bronchus (Fig. 1a and b). This finding prompted investigation and debulking of the lesion via bronchoscopy, revealing a fistulous connection between the esophagus and the right mainstem bronchus. Imaging via esophagogram confirmed a fistulous tract between the esophagus and the posterior right middle lobe (Fig. 2a and b). Pathology from the biopsy during bronchoscopy revealed a calcified fungus ball, filamentous bacteria with cultures positive for *Actinomyces*, and a broncholith secondary to *Candida* infection (Fig. 3a and b). Due to

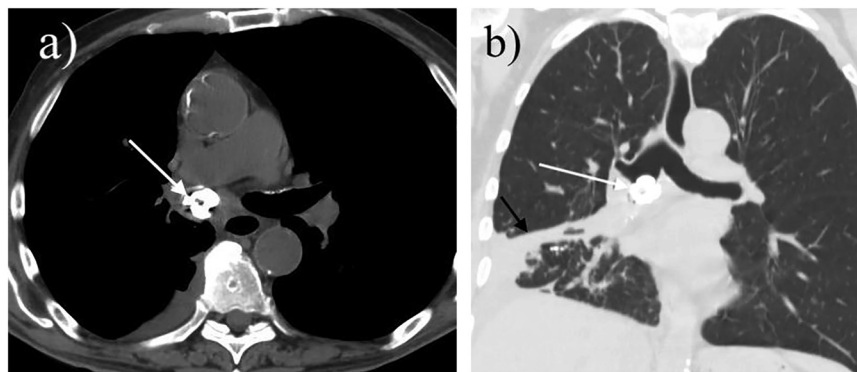


Fig. 1. Non-contrast computed tomography examination of the chest in axial (a) and coronal planes (b). A broncholith is present within the right mainstem bronchus (white arrow). Note is made of post obstructive right lower lobe atelectasis (Fig. 1b; black arrow)

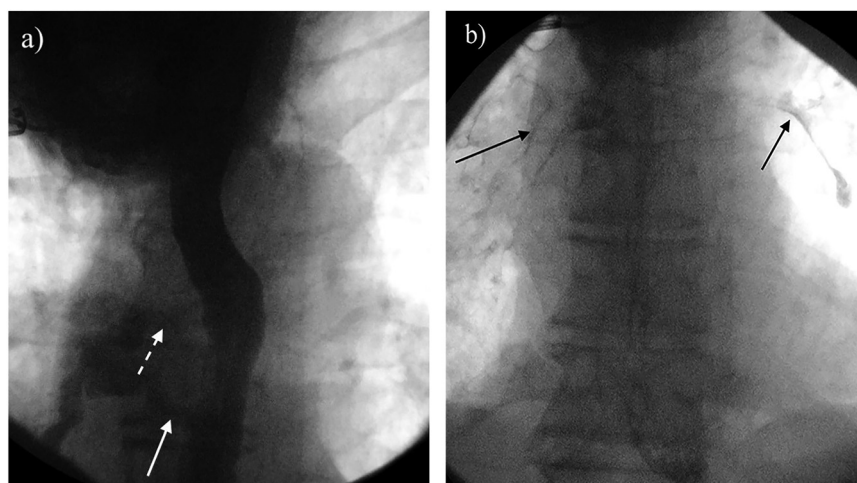


Fig. 2. Upper gastrointestinal examination with water soluble contrast. (a) Contrast opacifies a communication from the esophagus to the right mainstem bronchus (broken white arrow) consistent with bronchial esophageal fistula. (b). Delayed image demonstrating contrast within the central bronchial tree (black arrows) bilaterally

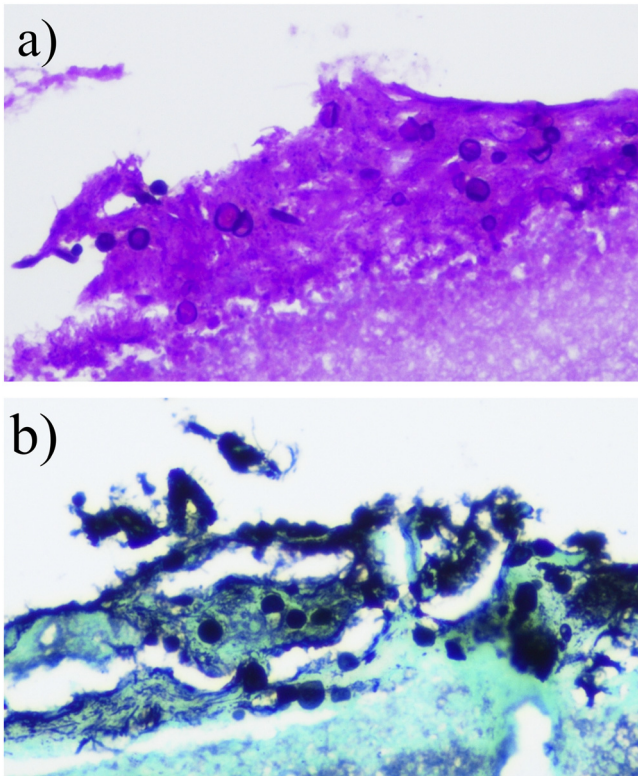


Fig. 3. Histology consistent with *Candida*. (a) Periodic acid Schiff (PAS) stain (400X) illustrating necrotic tissue and yeast forms consistent with *Candida* species. PAS allows for identification of basement membranes, glycogen, and mucopolysaccharides groups so that the morphology can be determined. (b) Grocott-Gomori methenamine silver (GMS; 400X), a specific stain to detect fungi by binding to the polysaccharides in the cell walls, identified yeast forms consistent with *Candida* species

the complexity of this presentation and the culture results, surgical treatment commenced; a right thoracotomy with right lower lobe wedge resection and repair of the TEF using an intercostal muscle flap was completed.

The postoperative course was uncomplicated, and the patient was extubated on postoperative day one (POD1) and transferred out of intensive care on POD2. By POD8, the patient resumed a modified oral diet, and based on the microbial cultures, was treated with a six-month course of amoxicillin-clavulanate and fluconazole. At a follow-up visit, the patient was eating well and had a resolution of sputum production and daytime dyspnea. A repeat bronchoscopy performed two months later showed normal mucosa without the presence of a fistula tract.

DISCUSSION

TEF are abnormal connections between the esophagus and the upper respiratory tract defined as either congenital or acquired, with the latter divided into malignant or benign entities (Fig. 4) [2, 3]. Most acquired TEFs in adults arise from advanced esophageal or bronchogenic malignancy

Bronchial-esophageal Fistula

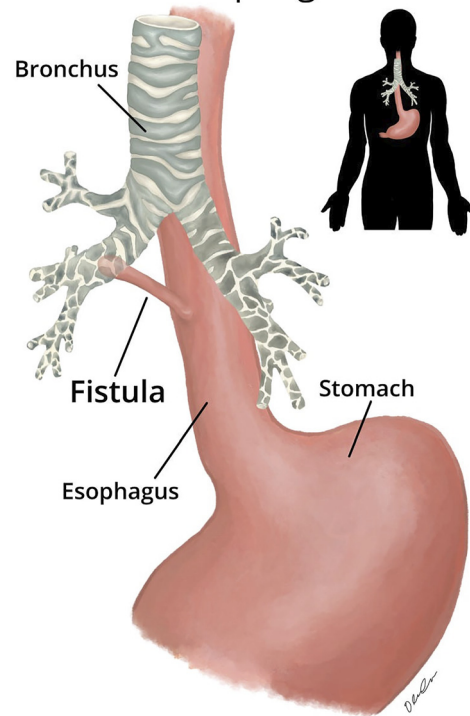


Fig. 4. Illustration of tracheoesophageal fistulas (TEF). Note the abnormal connection between the esophagus and the upper respiratory tract

[2, 3]. While benign TEFs are most commonly caused by granulomatous mediastinal infections, such as tuberculosis, 75% are secondary to complications of mechanical ventilation, traumatic intubation, or airway suctioning [1-3, 6, 10, 11]. An increased incidence of infection, such as immunosuppression, diabetes, and corticosteroid use, or prior airway infections are considered risk factors for TEF development [2, 3]. While our patient was not immunocompromised, he did have a significant tobacco smoking history (>50 pack-years), as well as a history of recurrent pneumonia, which may have contributed to the TEF [2].

TEFs are often asymptomatic and diagnosed as incidental findings on CT or bronchoscopy, but patients with TEF who are symptomatic often follow an insidious and progressive course [1-3]. Symptoms commonly include cough (56%), aspiration (37%), fever (25%), and dysphagia (19%), and may result in recurrent pneumonia, ARDS, and sepsis in those not diagnosed and treated correctly [2, 3]. Benign TEFs can often be definitively corrected with surgical intervention; however if a concurrent or underlying infection is not treated appropriately, there are higher rates of failure, recurrence, and complications [1-3]. Thus, the prompt and correct identification of the fistula and its etiology is paramount in treating those with TEFs.

Candida and actinomyces

The most common infectious cause of benign acquired TEF is granulomatous infection, most often tuberculosis

(Tables 1 and 2) [2, 3, 5–7]. Individual case reports noted 35.5% ($n = 11$) of fistula cases were attributed to infectious causes, with tuberculosis being the most common (72.7%, $n = 8$; Table 1). Other less common causes include agents of mucormycosis, herpes simplex infections, and *Candida* spp. infection, often in the setting of a compromised immune system or diabetes [12–14]. There have only been 12

published cases of TEF caused by *Candida* (Tables 3 and 4); seven individual reports and two reviews note *Candida* coinfection with *Actinomyces*, six of which confirmed the infections by culture (Tables 5 and 6). *Candida* and *Actinomyces* species can be found in the oral mucosa, often found in dental plaques and among normal mouth flora, typically causing infection in individuals with impaired

Table 1. Case reports of documented Bronchial Esophageal Fistula

Author	Year	Age	Sex	Symptoms	Comorbidities	Imaging	Findings	Type of fistula	Etiology	Treatment	Outcomes
Eroglu	2016	30	F	Dysphagia		EGD, bronchoscopy	Fistula of proximal esophagus	TEF	Pulmonary tuberculosis	Surgical repair w/ sutures, anti-TB Rx, CRT	
Lee	2016	51	M	Cough w/ aspiration	AML, CRT, neutropenia	Bronchoscopy, EGD, CT	Fistula w/ necrotizing PNA in RML/RLL	BEF	Pulmonary mucormycosis	AmpB, surgical excision	Hemoptysis, death
Garcia-Henriquez	2016	55	M	Cough, vomiting, dyspnea, leukocytosis		EGD, bronchoscopy	Clear mucus coming into the airway from fistula	TEF	Esophageal adenocarcinoma	Stent, endoscopic clip, R thoracotomy	Stent migration, atelectasis, death
Bertheuil	2017	52	M		Esophageal SCC, alcoholism, emphysema			TBF	Post-op complication	Surgical repair w/ intercostal muscle flap	D/c POD 24
Sato	2016	59	M	Progressive respiratory failure	Esophageal SCC	CT		TEF	Post-op complication	Surgical repair w/ latissimus dorsi flap, SEMS	Stent migration, bronchial artery aneurysm rupture, death
Kim	2016	49	M	Aspiration PNA, chronic cough	Tuberculosis	EGD, CT, endoscopy		BEF	Incidental finding	Surgical repair	
Kebbe	2017	43	M	Chronic PNA, hemoptysis		CT, EGD	Sub-carina calcification w/ EPF	EPF	Migration of mediastinal calcifications	Surgical repair	
Kumar	2017	26	M	Chronic cough, dysphagia, aspiration PNA	Tracheal stenosis, prolonged intubation	CXR, CT, bronchoscopy	Mucosal bulge obscuring stent, fistula track	BEF	Stenting complication	Surgical repair w/out stenting	D/c POD 7
Martins	2017	57	F	Dysphagia, chronic cough, fever, weight loss		CXR, CT, GSS bronchoscopy, endoscopy	Fistula below carina w/ opacification of the R bronchial tree to R lung, fistula in esophagus	BEF	Tuberculosis	Anti-TB Rx, endoscopic clip	Fistula recurrence
Alexander	2017	27	F	Productive cough, dysphagia		Bronchoscopy, endoscopy, CXR, CT, GSS	2 fistulas	TEF	Tuberculosis	Ivor-Lewis procedure, intercostal muscle flap	D/c POD 14
Indiran	2017			Chronic cough	Post-renal transplant	CT		BEF	Pulmonary Tuberculosis		
Munikoty	2017	10	F		Pulmonary Tuberculosis			TEF	Hodgkin Lymphoma	Anti-TB Rx, CRT	
Omori	2017	72	M	Worsening oxygen saturation post-op		CT, bronchoscopy	Aeration in RML/RLL, broncho-cutaneous fistula, stent migration	EPF	Post-op complication	Surgical repair w/ latissimus dorsi flap, R lobectomy	Stent displacement, fistula recurrence
Sayeed	2017	21	M	Dysphagia, dyspnea, odynophagia, weight loss	Chronic aspiration PNA, bronchiectasis	CT, CXR, EGD, bronchoscopy	Fistula connecting LMB and esophagus, frothy secretions	BEF	Pulmonary Tuberculosis	Endoscopic clip, anti-TB Rx	
Zhang	2017	69	F	Acute worsening of chronic cough, dysphagia	Tuberculosis	EGD, endoscopy, CXR, CT	2 fistulas between middle esophagus and LMB	BEF	Silicosis w/ broncholithiasis	Esophageal stent, antibiotics	Stent ulceration, persistent fistula
Buemi	2018	72	M	Hoarseness, dyspnea, PNA	Testicular seminoma, lung cancer	CXR, CT, fluoroscopy	Air in mediastinum, fistula of upper third esophagus	EPF	CRT complication	SEMS	
Alsaadi	2018			Tachypnea, decreased air sounds on right side	Anorectal malformation, esophageal atresia	Endoscopy, CT	Reflux of contrast into anomalous airway	TEF	Intubation complication		
Alharbi	2019	19	M	Chronic cough, hemoptysis	Mediastinal bronchial artery aneurysm	CT, endoscopy, bronchoscopy	Fistula in mid-esophagus	EMF	Mediastinal Tuberculosis	Trans-arterial embolization	
Li	2019	50	M		Diabetes, esophageal SCC	CT, bronchoscopy	Connection between intermediate bronchi, white necrotic material	TBF	Mediastinal tube compression w/ fungal infection	Anti-fungal Rx, SEMS	
Favere	2019			Pulmonary sepsis, respiratory failure	Esophageal malignancy	Bronchoscopy	Presence of fistula	GBF	Surgical complication		Death
Hajjar	2019	47	M	Chronic chest infection, productive cough, fever, weight loss,	Adrenocortical insufficiency	Endoscopy, CT, barium swallow	Narrow fistula tract from LLL to esophagus	BEF	Pulmonary tuberculosis	Surgical repair w/ suture, anti-TB Rx	
Ohsawa	2019	44	M	PNA	Esophageal bypass, CRT w/ cisplatin, 5FU			BEF	Esophageal cancer	Surgical repair w/ bypass	

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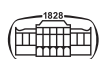


Table 1. Continued

Takasugi	2019	70	M	Dysphagia				BEF	Esophageal cancer	Surgical repair w/ colonic transplant	Reflux esophagitis
Tautz	2019	28	M	Abdominal pain, nausea, vomiting, atypical PNA, ARDS		CT, EGD	Bronchial opening of fistula	BEF	Pulmonary Tuberculosis	Anti-TB Rx, antibiotics, surgical resection w/ intercostal muscle flap, stent	Fistula recurrence, bilateral hemorrhagic pleural effusions
Vachtenheim	2019	46	M	Acute necrotizing mediastinitis, aspiration, non-productive cough	Odontogenic abscess, purulent mediastinitis, tracheostomy	EGD, bronchoscopy	Fistula in LMB	BEF	Surgical complication	Surgical repair w/ bypass, SEMS	Esophageal stricture leak, fistula recurrence
Khitaryan	2019	52	F	Dysphagia, retrosternal pain, nausea, weight loss	Esophageal SCC	EGD, CT	Esophageal mass w/ fistula	TPF	Surgical complication	Surgical repair w/ suture	
Arora	2020	56	M	Respiratory distress, subcutaneous emphysema	Hypopharynx carcinoma post-CRT			TPF	Surgical complication	Bronchoscopic removal, R thoracotomy w/ latissimus dorsi flap	
Ahmed	2020	71	F	Dyspnea, fever, chills, chest pain, dysphagia	HSV esophagitis, tobacco use	CT, EGD, bronchoscopy	Pneumomediastinum, focal contrast extravasation, fistula in LLL	EBF	HSV-1 esophagitis	Partially covered SEMS, VATS, IV acyclovir	
Miyata	2020	64	M			CT, bronchoscopy	Bubbles of saliva through fistula w/ swallowing	GTF	Surgical complication	Surgical repair w/ intercostal muscle and latissimus dorsi flap	
Sonomura	2021	64	M	Fever, cough	Esophageal cancer	CT, fluoroscopy, endoscopy	Anastomotic leak, fistula	BEF	Surgical complication	Stent, endoscopic clip, OTSC, argon plasma coagulation	
Yanagihara	2021	88	F					BEF	Esophageal foreign body	Surgical repair w/ sutures, L thoracotomy w/ intercostal muscle flap	D/c POD 11

Grey boxes indicate information not available in the report; ARDS – Acute Respiratory Distress Syndrome; AML – Acute Myeloid Leukemia; AmpB – Amphotericin B; CRT – Chemoradiation Therapy; GSS – Gastrografin Swallow Study; OTSC – Over-The-Scope Clipping; PNA – Pneumonia; SCC – Squamous Cell Carcinoma; SEMS – Self-Expanding Metallic Stent; VATS – Video-Assisted Thoracic Surgery; LLL – Left Lower Lobe, LMB – Left Main Bronchus, RML – Right Middle Lobe, RLL – Right Lower Lobe; TEF – Tracheoesophageal Fistula; TBF – Tracheobronchial Fistula; BEF – Bronchioesophageal Fistula; EMF – Esophageal-Mediastinal Fistula; EPF – Esophageal-Pulmonary Fistula; GTF – Gastro-Tracheal Fistula; GBF – Gastro-Bronchial Fistula.

mucosal barriers or compromised immune systems [15, 16]. While isolated *Candida* infections can occur, *Actinomyces* rarely is the sole culprit of infection, instead, it is often part of a microbial infection in conjunction with other species like *Streptococcus*, *Fusobacterium*, or *Candida* [15, 16]. While there are several reports of *Candida* and *Actinomyces* co-infection resulting in esophageal or pulmonary infection, only one noted the formation of a fistula (Table 5) [17]. Like tuberculosis, actinomycosis causes chronic granulomatous inflammation, which may have contributed to the fistula formation in our patient [15, 16]. *Actinomyces* is a known etiology of mycetoma, chronic granulomatous infections that are classically difficult to treat and require prolonged therapy [8, 9]. These are characterized as either fungal (eumycetoma) or bacterial (actinomycetoma), as in the case of our patient, and classically present with small, painless subcutaneous nodules that develop purulent discharge [8, 9]. Our patient was unusual, not only in the presentation of their actinomycetoma but in its co-infection with *Candida* and its complication by the formation of a broncholith and subsequent fistula, which, to our knowledge, has not been previously described.

Actinomycetoma and broncholithiasis

Broncholithiasis is caused by calcification of material that enters the tracheobronchial tree, often due to granulomatous infection material that migrates from surrounding lymphatic

structures [4, 5]. This can result in airway obstruction and inflammation, and while most often asymptomatic, they can be complicated by recurrent pneumonia and TEF formation [4, 5]. In fact, it was found that the most common infectious causes were fungal and mycobacterial infections, with *Histoplasma* being the most common etiology in the United States and other less common pathogens being tuberculosis, *Actinomyces*, and *Aspergillus* [4]. Despite the association with actinomycosis, there has not been a reported case of the formation of an actinomycetoma with *Candida* co-infection further complicated by broncholithiasis and TEF, representing a novel presentation for this pathology.

Diagnosis of TEF

Currently, there are no formal guidelines to establish or confirm the diagnosis of TEF. However, most experts agree that either esophagography or endoscopy is necessary to diagnosis and assist with pre-operative planning [2, 18]. The diagnosis of TEF is most often made using a combination of upper endoscopy and bronchoscopy. The literature review noted that 67.7% ($n = 21$) of patients were initially evaluated with CT, followed by bronchoscopy (41.9%, $n = 13$) and an esophagogastroduodenoscopy (EGD; 35.5%, $n = 11$; Table 1) [1, 2, 18]. CT initially only revealed a broncholith in our patient, but follow-up upper endoscopy revealed a fistulous communication between the right mainstem bronchus and the esophagus (Fig. 2a and b). While not necessary,

Table 2. Review articles reporting Bronchial Esophageal Fistula

Author	Year	Mean Age	Cohort Size	Sex Ratio	Symptoms	Comorbidities	Imaging	Location	Etiology	Treatment	Outcomes
Cao	2015		9	M 7 F 2				BPF (7) TPF (1) BEF (1)		Fully covered SEMS	Thoracic empyema (8), 2 deaths
Hihara	2016	64	16	M 12 F 4				BEF (1)	Esophageal SCC, CRT w/ docetaxel and 5FU		
Lambertz	2016	57	1204	M 11 F 2	Leak on exam, respiratory, cardiovascular failure	Squamous cell carcinoma (6), adenocarcinoma (7)	Bronchoscopy, EGD	TEF (13) - LMB (6) RMB (2) trachea (5)	Ivor-Lewis esophagectomy	Re-thoracotomy (7), endoscopic (10), bronchoscopic therapy (4)	5 deaths from sepsis, respiratory failure, PNA
Li	2016		10	M 10 F 0	Dysphagia w/ solids and liquids, fever (2), hemoptysis (2)	Esophageal cancer	CT, bronchoscopy	GTF (10) - LMB (4) RMB (4) trachea (2)	Esophagectomy, tumor recurrence, radiation, erosion of staple	Covered metallic stent, Y-shaped SEMS	Leakage, stent displacement, 6 deaths – tumor recurrence (5) lung infection (1)
Nasir	2016	64	39	M 22 F 17	Esophageal obstruction	Esophageal cancer, lung cancer	Esophagogram, endoscopy, CT	TEF (15) - proximal trachea (6) carina (6) bronchus (3)	Malignancy	Combined airway and esophageal SEMS (20), silicone stent (5), bifurcated silicone stent (8)	Feeding tube (11), PEG tube (10), 5 deaths – PNA (3) heart failure (1) perforation (1)
Wlordarczyk	2016				Dysphagia, weight loss			BEF (10%)	Esophageal SCC	Stenting, laser therapy, chemoradiation, photodynamic therapy, pre-surgical dilation	Peri-op mortality 0-5%, 30-day mortality 7-18%
Udelsman	2016	54	8	M 3 F 5		Prior esophageal, tracheal, thyroid surgery, HIV/AIDS esophagitis, malignancy, esophageal stenosis	Bronchoscopy, CT, EGD	TEF (4) – LMB (2) trachea (3) BEF (1)	Malignancy, stent erosion, post- intubation injury	Right thoracotomy (4), cervical/median sternotomy (1) - latissimus dorsi (2) intercostal flap (1) omentum (2)	Tube dependence (2), chronic PNA, dehiscence
Yang	2016	40	30				Endoscopy, bronchoscopy, Barium study, CT	TEF	Recurrent TEF, post-intubation injury, trauma, foreign body, stents, prior esophageal surgery, caustic ingestion	“double-patch” surgical closure	Fistula recurrence, anastomosis, PNA
Chang	2017	70	64	M 42 F 22				BEF (1)	NSCLC (17%) w/ proton beam therapy, SCC (44%), Adenocarcinoma (39%)		
Inage	2017		2	M 2 F 0	PTX, post-op PNA	Esophageal cancer	CT, fluoroscopy	GBF	Esophagectomy	Endoscopic bronchial occlusion	Pleural infection, aspiration PNA, respiratory failure, atelectasis
Han	2017	59.1	63	M 52 F 11	Dysphagia, chronic PNA	Esophageal cancer, cardiac cancer	Bronchoscopy, gastroscopy, endoscopy, CT	GTF – trachea (12) carina (14) LMB (21) RMB (15) RIB (1)	Esophagectomy	Esophagectomy, endoscopic stent – SEMS (9) Y-SEMS (41) Y-paired SEMS (13)	Incomplete fistula closure (4), 15 deaths - infection (1) metastatic dx (13) hemoptysis (1),
Diekhoff	2017	56	15	M 10 F 5		NSCLC		EPF (3)	Post- CRT complication	Esophagectomy	Jejunal ischemia (1), bleeding (1), multiple operations (3)
Fricke	2017	55	13	M 10 F 3		Recurrent aspiration PNA (4), sarcoidosis, cachexia (7), tuberculosis, COPD (5), Hep B, HIV		BPF (2) TEF (1) GBF (1) BEF (1) Bronchus (5) trachea (2) esophagus (2)	Esophageal cancer (5), NSCLC (2), pleural mesothelioma, gastric cancer, COPD, esophageal erosion – empyema from <i>Candida</i> (5), pseudomonas (4)	Surgery w/ flap - latissimus dorsi (18) pectoralis major (7) rectus abdominis (1) intercostal (1)	Fistula recurrence (5), bronchial fistula (1), post-op hemorrhage (1), peri-op death (1), recurrent pleural empyema (2)
Roskopskova	2017	53	22	M 15 F 7	Malnutrition, sepsis, shock, chronic PNA	Prior radiation or chemotherapy (64%), prior airway or esophageal stenting (50%)	Bronchoscopy	TEF – trachea or carina (8) RMB (4) LMB (3)	Esophageal surgery complication (18), Boerhaave syndrome (1), CRT (1), carinal resection (1), laryngectomy (1)	Surgery w/ flap (12), lobectomy (4), resection/anastomosis (2), pneumonectomy (1), segmentectomy (2), primary suture (1)	Chronic PNA (1), AEF (1), mesenteric ischemia (1) - TEF recurrence 4.5%, 90-day POD mortality 18%
Silon	2017	65	25	M 15 F 10	Aspiration		Endoscopy, CXR	EPF- esophagus proximal (12) mid- (5) distal (6)	Surgery complication (6), CRT (1), malignancy (14) – esophageal adenocarcinoma (4), SCC (3), lung cancer (4), large B cell NHL (2), small cell neuroendocrine tumor (1)	Esophageal stents (6), OTSC (5), SEMS (23) – fully covered (20) partially covered (3)	Stent migration (5), dysphagia (1), site bleeding (1), PNA (1)

(continued)

Table 2. Continued

Zhou	2017					Coughing w/ swallowing, purulent bronchitis, PNA		Barium or gastrograffin swallow study, endoscopy	TEF	Esophageal/Upper respiratory carcinoma, surgery, CRT	Chemotherapy, radiation, airway stents, self-expanding stents, silicone stents, double stents	Malnutrition, infection, sepsis, NG Tube or J-tube placement
Balakrishnan	2018		11	M 6 F 5		Sepsis, respiratory failure	Esophageal SCC (4), adenocarcinoma (4), Granular cell tumor (1), neuroendocrine tumor (1), tracheostomies (4), laryngeal resection (2), jejunostomy (8)	Endoscopy, bronchoscopy, CXR	TBF	Esophagectomy w/ anastomotic leak or necrosis (6), staple line erosion (1), stricture dilation (1), recurrent esophageal cancer (1)	Primary repair, muscle or omental flaps (8), bio-prosthetic patch (2), sleeve resection of bronchus (1)	Recurrent fistula (2), 3 post-op deaths – post-TEF repair (2) PNA (1)
Blatter	2018	59	73	M 50 F 23			Malignancy (81%), chemotherapy (58%)	Bronchoscopy	BPF (17) TEF (7)		Surgical reconstruction w/ muscle flap - latissimus dorsi (48) serratus anterior (23) pectoralis major (7)	3 deaths
Lee	2018	56	19	M 14 F 5					BEF (2) – upper esophagus (1), mid-esophagus (1)	Esophageal cancer (1), pulmonary tuberculosis (1)	OTSC	
Sersar	2018	29	27	M 11 F 16		Dysphagia, tachycardia, chronic PNA			TEF (8) BEF (6) EPF (5)	Post-endoscopy (4), iatrogenic, esophageal cancer, blunt chest trauma		6 deaths – esophageal cancer (5) airway obstruction (1)
Still	2018	63	13	M 6 F 7				CT, esophagram, endoscopy	EBF (2)	Bilateral lung transplantation dehiscence, esophageal stricture w/ balloon dilation	EVAC therapy, stent	
Wlondarczyk	2018	61	46	M 37 F 7		Dysphagia, dyspnea		CXR, CT, esophagoscopy, bronchoscopy	EPF – trachea (20) MB (24) RMB (2)	Advanced lung and esophageal cancer (10%)	SEMS, silicone Stenting – unilateral (20) double (26)	recurrence of fistula, massive fatal hemorrhage, stent migration
Debourdau	2019	58	22	M 13 F 9		Aspiration PNA, post-prandial cough, mediastinitis, recurrent COPD exacerbations	Previous thoracic radiation, esophageal stricture (6), tracheal stenosis (2)	Endoscopy	TEF (17) – RMB (3) LMB (2) EPF	Surgery (12), esophageal dilation (3), invasive ventilation (3), radiation therapy (2), tracheostomy (2)	Endoscopic stent (21), OTSC (8), combined (7)	Endoscopic success (10), functional success (2), endoscopic failure (10), 6 deaths
Akram	2020	47	51	M 24 F 27			Bronchial stenosis (18), tracheal stenosis (11)		TEF (13)	Esophageal cancer (37), lung cancer (6)	Endoscopic stenting	
Asaad	2020		198						BPF (156) TEF (48)	Surgical complication	Surgical repair w/ pedicled muscle flaps	BPF (34), esophageal fistula (13)

Grey boxes indicate information not available in the report; CRT – Chemoradiation Therapy; EVAC – Endoluminal Vacuum; NHL – Non-Hodgkin Lymphoma; NSCLC – Non-Small Cell Lung Cancer; OTSC – Over-The-Scope Clipping; PNA – Pneumonia; PTX – Pneumothorax; SCC – Squamous Cell Carcinoma; SEMS – Self-Expanding Metallic Stent; RIB – Right Intermediate Bronchus; RMB – Right Main Bronchus; LMB – Left Main Bronchus; TEF – Tracheoesophageal Fistula; TBF – Tracheobronchial Fistula; TPF – Tracheopulmonary Fistula; BEF – Bronchioesophageal Fistula; BPF – Bronchopulmonary Fistula; EPF – Esophageal-Pulmonary Fistula; GTF – Gastro-Tracheal Fistula; GBF – Gastro-Bronchial Fistula; AEF – Aorto-Esophageal Fistula.

radiographic imaging with chest radiography is often obtained in the setting of aspiration pneumonia or other symptoms suggestive of consolidation, and this may show non-specific signs of aspiration-related changes, lung masses, or widening of the mediastinum in the setting of granulomatous disease [1–3, 18]. CT imaging of the chest may be used to evaluate for signs of fistula or abnormalities in the mediastinum or aerodigestive tract; currently, there is a lack of data regarding the sensitivity, specificity, or predictive values of CT imaging in patients with known TEF [2]. CT imaging is useful, however, and plays a crucial role in diagnosing broncholithiasis, as it can give information on the location and degree of obstruction. While CT has good sensitivity for the early detection of bone involvement in those with more classic mycetoma of the lower extremity, in those cases, it is less frequently used as part of the routine diagnostic work-up in favor of culture and histology [4, 8]. In our patient, non-contrast CT of the chest revealed a broncholith within the right mainstream bronchus with evidence of post-obstructive atelectasis in the right lower lobe (Fig. 2).

Treatment of infections in TEF

While treatment of TEFs is often aimed at treating the fistulous communication, concomitant efforts need to be made to treat the underlying cause. Although infectious causes of benign acquired TEF are not uncommon, the treatment and diagnosis are not well described. The most commonly described infectious cause of TEF was tuberculosis infection, which, once confirmed as secondary to infection with *Mycobacterium tuberculosis*, is typically treated with surgical repair and prolonged courses of combination antibiotics [2, 5–7, 19]. Other infectious causes that have been recently described include mucormycosis infection treated with liposomal amphotericin B and a case of silicotuberculosis infection [5, 17]. Broncholithiasis is managed surgically or conservatively based on patient symptoms and extent of disease, with definitive management consisting of bronchoscopic extraction or pulmonary resection of the affected lobe [4, 5]. Unlike broncholithiasis, surgical treatment alone of mycetoma is rarely successful, but does play a role in fungal disease [8]. The pharmacologic treatments vary based on the

Table 3. Case Reports of documented *Candida* Fistulas

Author	Year	Age	Sex	Symptoms	Comorbidities	Imaging	Histology	Type of fistula	Treatment	Outcomes
Sehhat	1976	28	M	Dysphagia, dyspnea, chest pain, productive cough, weight loss		Barium swallow	Yeast-like cells, white necrotic tissue	EPF	Right lobectomy, esophagectomy, streptomycin, AmpB	Abscess
Obrecht	1984	22	F	Fatigue, hematochezia, non-productive cough, dyspnea	HSV esophagitis, leukemia	Barium swallow, EGD	Ulcers, granular mucosa, confluent white plaques	TEF	Mycostatin	Hematemesis, cardiac arrest, death
Rusconi	1994	35	M	Dyspnea, non-productive cough	HIV, CMV esophagitis	Bronchoscopy	Infiltrating, vegetative mass	TEF		Death
Lew	1995	25	M	PNA, atelectasis, respiratory failure, septic shock	Spine surgery	CT, barium swallow		EPF	AmpB	Dislodgement of graft, death
Rassl	2000	52	M	Hemoptysis	Coronary artery bypass			ABF		Aortic dissection, graft infection, death
Thibodaeu	2007	49	M	Chronic PNA, abdominal pain, dysphagia, fever	Esophageal perforation, PUD	Esophagogram endoscopy, CXR	Irregular friable mucosa w/ purulent drainage	EPF	Levofloxacin, fluconazole, esophagectomy	D/c POD14
Al-Shawwa	2008	7	M	Fever, dyspnea, oliguria, hypoxia, respiratory failure		CXR, endoscopy		EPF	Cefotaxime, vancomycin, AmpB, esophagectomy	Chronic empyema
Kanzaki	2009	70	M	Dysphagia, weight loss, chest pain, high fever		Endoscopy, CT, bronchoscopy	Linear white plaques, yeast-like cells	EPF	Esophageal bypass, AmpB, fluconazole, itraconazole	Abscess, chronic PNA, death
Tang	2009	47	M	Fever, chills, abdominal pain	Gastric cancer, CRT	CXR, CT, EGD	Fistula opening at ulcer base	Gastro-pericardial fistula	IV fluconazole	Pneumoperitoneum
Pentiak	2011	64	M	Hematemesis	PUD, chronic PPI use, esophageal perforation, post-esophagectomy	Endoscopy, CT		Gastro-cardiac fistula	Surgical repair	Hemorrhage, death
Tonetti	2012	86	F	Abdominal pain, rectal bleeding		Colonoscopy, CT		Peri-rectal fistula	Pip-tazo, fluconazole	D/c POD14
Koncar	2016	69	M	Chest pain, hemoptysis, weight loss, PNA	Endovascular aortic aneurysm repair	CT, EGD		ABF	Graft replacement, esophagectomy	Stent infection, Death
Matta	2019	43	M	Chest pain		ECHO, CT, EGD		EPF	Surgical repair, po fluconazole	Pericarditis w/ effusion
Rizkalla	2020	55	M		Liver cirrhosis, hepatorenal syndrome	CXR, US		Colo-vesicular fistula		Variceal bleeding
Siroky	2020	71	M	Chest pain, bacteremia	Pulmonary vein isolation	CTA, ECHO, Barium swallow		PEF	Endoscopic stenting, suture fixation	Pneumopericardium, pericardial abscess, death
Georgeades	2021	64	M	Abdominal pain, back pain, weight loss, night sweats	Endovascular aneurysm repair, latent TB	CTA, EGD	Ulcer w/ visualization of graft	Aortic-duodenal fistula	Surgical resection, micafungin, daptomycin, fluconazole	Death
Meiwandi	2021	58	M	Chronic surgical site infection	Esophageal cancer, esophageal resection, gastrectomy	CT		Osteo-cutaneous fistula	Caspofungin, po fluconazole, surgical resection w/ latissimus dorsi flap	Chondro-osteomyelitis
Meiwandi	2021	81	F	Chronic surgical site infection	Thoracotomy, sleeve gastrectomy	CT		Osteo-cutaneous fistula	Fluconazole, surgical repair w/ latissimus dorsi flap	Chondro-osteomyelitis

Grey boxes indicate information not available in the report; AmpB – Amphotericin B; PNA – Pneumonia; PUD – Peptic Ulcer Disease; TEF – Tracheoesophageal Fistula; PEF – Pericardial-Esophageal Fistula; EPF – Esophageal-Pulmonary Fistula; ABF – Aorto-Bronchial Fistula.

Table 4. Review articles of *Candida* Fistulas

Author	Year	Mean Age	Cohort Size	Sex Ratio	Symptoms	Comorbidities	Imaging	Type of fistula	Etiology	Treatment	Outcomes
Ackerman	1975		23			Multiple antibiotics, surgeries, advanced age, debility, cancer, ESRD		Biliary or intestinal fistula			
Sato	2017	64	142	M 92 F 50	Hemorrhage	Pancreatic cancer		Pancreatic fistula	Complication of pancreaticoduodenectomy		Fistula (17%), positive cultures (24%), <i>Candida</i> , <i>C. albicans</i> w/ hemorrhage (8%), 6 deaths from hemorrhage
Mohamed	2019				Odynophagia, retrosternal pain	HIV/AIDS, diabetes, CRT, esophageal motility dx, chronic PPI use	EGD, histology, barium swallow	BEF	Esophageal candidiasis	AmpB, po/IV fluconazole, itraconazole, voriconazole, posaconazole	
Abe	2020	69	429	M 268 F 161	Fever, abdominal pain, hemorrhage	Tobacco use, advanced age, diabetes		Pancreatic fistula	Complication of pancreatotomy	Removal of drain, antibiotics	<i>C. albicans</i> seen in 29% of all infections, correlated w/ fistula, pseudoaneurysm, hemorrhage

Grey boxes indicate information not available in the report; CRT – Chemoradiation Therapy; PPI – Proton-Pump Inhibitor; TEF – Tracheoesophageal Fistula; BEF – Bronchioesophageal Fistula.

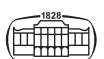


Table 5. Case Reports of documented *Actinomyces/Candida* Co-infection

Author	Year	Age	Sex	Symptoms	Comorbidities	Imaging	Findings	Histology	Cultures	Treatment	Outcomes
Arora	2003	37	M	Chest pain	AIDS	EGD, CT	Ulceration	Filamentous bacteria, sulfur granules	<i>Candida, Actinomyces</i>	IV PCN, po fluconazole	Esophageal <i>actinomyces</i> , death
Chou	2006	41	M	Dysphagia, odynophagia	EtOH use	EGD, CT	Ulceration	Filamentous bacteria, sulfur granules, budding yeasts	<i>Candida, Actinomyces</i>	IV PCN, po amoxicillin	Esophageal <i>actinomyces</i> , resolution of sx
Murchan	2010	53	M	Epigastric pain, odynophagia	AIDS, HCV, Pott's dx of spine, esophageal candidiasis	EGD	Ulceration	Filamentous bacteria		IV doxycycline	Esophageal <i>actinomyces</i> , death from pneumococcal PNA
Ghosh	2017	23	M	Fever	Previous nasal infection, tobacco, EtOH use	CXR, CT, Bronchoscopy	Lucent area in LML, pleural effusion, heterogenous mass	Filamentous bacteria, budding yeasts	<i>Candida, Actinomyces</i>	IV PCN, po fluconazole	Pulmonary actinomycosis
Zhang	2019	45	F	Dysphagia, weight loss, odynophagia		EGD, CT	Friable mucosa w/ ulceration	Filamentous sulfur granules, fungal hyphae		IV PCN, po fluconazole	Esophageal stricture
Baig	2020	79	F	Dysphagia, hematemesis	Inhaled corticosteroid use, COPD, SCLC	CT, EGD	Air fluid levels, friable mass w/ obstruction	Filamentous rods, sulfur granules w/ inflammatory exudates	<i>Candida, Actinomyces</i>	IV ceftriaxone, po fluconazole	Esophageal <i>actinomyces</i> , resolution of sx
Seifert	2020	32	M	Dyspnea, cough		CXR, CT, Bronchoscopy	Pneumo-mediastinum, subcutaneous air, RUL/RML consolidation	Necrotic tissue w/ fungal hyphae	<i>Rhizopus, Candida, Mucorales, Actinomyces</i> , +AFB	Vanc, Pip-Tazo, Doxy, Voriconazole, liposomal AmpB	Broncho-mediastinal fistula, necrotizing PNA, death

Grey boxes indicate information not available in the report; AFB – Acid-Fast Bacillus; PCN – Penicillin; PNA – Pneumonia; SCLC – Small Cell Lung Cancer; RML – Right Middle Lobe; RUL – Right Upper Lobe; LML – Left Middle Lobe.

Table 6. Review articles of *Actinomyces/Candida* Co-infection

Author	Year	Mean Age	Cohort Size	Sex Ratio	Symptoms	Comorbidities	Imaging	Histology	Cultures	Treatment	Outcomes
Santos	2004	50	2	M 0 F 2				Sulfur granules, budding spores w/ pseudo-hyphae			Acute suppurative cholecystitis
Urs	2016	38	5	M 5 F 0	Exposed necrotic bone (5), odynophagia (4)	Diabetes (2)	Xray, CT		<i>Candida</i> (3), <i>Mucor</i> (2), <i>Staph</i> (1), <i>Aspergillus</i> (1)	D&C (3), AmpB (2), fluconazole, itraconazole (2), metronidazole (3), surgical removal of sinus (3)	Fungal maxillary osteomyelitis

Grey boxes indicate information not available in the report; AmpB – Amphotericin B.

infectious agent; fungal mycetoma (eumycetoma) often requires combined surgical excision followed by prolonged therapy with itraconazole for 1–2 years as first-line therapy, whereas actinomycetomas are often amenable to antibiotic therapy alone [8]. Antimicrobial treatment options for actinomycetoma often include use of penicillins, aminoglycosides, trimethoprim-sulfamethoxazole, or dapsone alone or in combination with one another, partially depending on the organisms determined to be driving the process [8]. A commonly used regimen in our review was use of IV penicillin for *Actinomyces* involvement, with oral fluconazole when there is concern for fungal coinfection. A period of more intensive treatment can then be followed by oral amoxicillin (Table 5).

Although reported as an infectious cause of benign acquired TEF, there are currently no concise guidelines on treatment for patients with TEF secondary to *Candida* infection. Of the cases that noted fistulas attributed to *Candida* infection, 15 reported treatment, and of those, eight were treated with combined surgery and medical therapy (44.4%) with an associated 25% mortality. Another four

cases were treated with medical therapy alone (22.2%), with an associated 50% mortality and three patients were treated with surgery alone (16.7%), associated with a 100% mortality (Table 3). Of those that received medical therapy, the most commonly given antimicrobial agent was fluconazole ($n = 8$) followed by amphotericin B ($n = 4$), consistent with other reports [20]. To date, complications following treatment for infectious causes of fistulae have not been reported (Table 4). Only one reported case of an *Actinomyces* and *Candida* co-infection that resulted in a fistula has been reported; treatment was a combination of vancomycin, voriconazole, piperacillin-tazobactam, and liposomal amphotericin B and was complicated by *Mucorales* and *Rhizopus* infection, resulting in necrotizing pneumonia [17]. Our patient's definitive therapy was a combination of amoxicillin-clavulanate and fluconazole for six months based on the *Actinomyces* and *Candida* co-infection; a wedge resection and flap reconstruction was also completed without any perioperative morbidity. Follow-up esophagography suggested no leak from the fistula site, and all symptoms have resolved.

Diagnostic Algorithm

Based on the comprehensive literature review and the current management practices of benign acquired TEF, a diagnostic algorithm is proposed to assist in better diagnose those with relevant symptoms and history (Fig. 5). Once diagnostic imaging confirms the presence of a TEF, the

anatomy should be further evaluated with esophageal and bronchial endoscopic visualization. Endoscopic evaluation allows for visualization and characterization of the fistula, can be used to dislodge debris obstructing the fistula site and assist in obtaining crucial biopsies of the lesion to help determine the underlying etiology of the TEF, guiding its treatment [1, 2, 4, 9, 10, 17, 18].

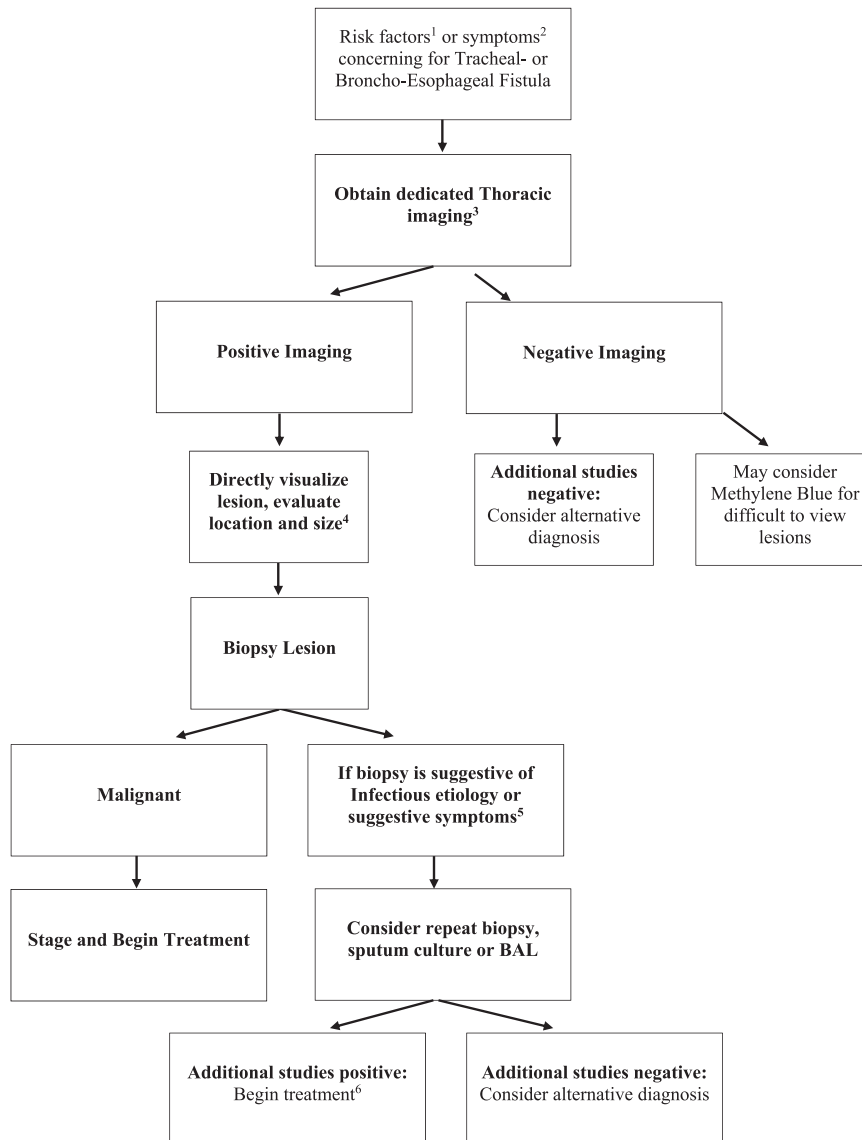


Fig. 5. Diagnostic algorithm

¹Risk factors include history of esophageal or bronchial malignancy, prior surgery or stenting, HIV/AIDS, TB, prior radiation

²Symptoms suggestive of TEF or EBF include cough (56%), aspiration (37%), fever (25%), dysphagia (19%), PNA (5%), hemoptysis (5%), or worsening of cough with swallowing liquids and solids 87% (Ono's Sign)

³Imaging includes Esophagography (1st line), barium preferred over gastrograffin (70% accurate), CT is preferred in those that cannot swallow, those that are ventilated or intubated that present with continued air-leaks despite well-inflated cuff, abdominal bloating, loss of tidal volume or worsening oxygenation

⁴Positive imaging should be followed up with Endoscopy or Bronchoscopy (flexible or rigid), as both will directly visualize lesion, evaluate location and size of lesion and can be used to get biopsy

⁵Symptoms suggestive of infectious etiology include additional symptoms of weight loss, night sweats or infection refractory to standard therapy

⁶Common infectious causes include tuberculosis, mucormycosis, histoplasmosis, syphilis, aspergillosis, each with specific biopsy findings, risk factors and treatments

Traditionally, TEF is repaired with an endoscopic approach, preferable to open surgical approaches, as endoscopy has a much lower risk of fistula complications [1, 3, 21]. Benign TEFs are often amenable to definitive surgical intervention compared to those with TEF secondary to malignancy, which often have multiple comorbidities that make them poor surgical candidates [1–3]. The primary endoscopic technique is esophageal or airway stenting, using self-expanding plastic stents that primarily serve as a bridge to definitive surgical repair, especially in those with concomitant tracheal stenosis in order to maintain airway patency [1, 12, 18, 22, 23]. Stenting can also be used in those with benign TEF that are not surgical candidates, opting for a single stent in those with distal fistula sites, or dual stenting those with more proximal or mid-esophagus fistulae [1, 12, 18, 22, 24–26]. Although self-expanding metallic stents (SEMS) are usually preferred for those with malignant fistulae, there is a growing body of evidence that prefers fully covered SEMS in those with complicated benign TEFs or those who are not surgical candidates [1, 12, 18, 22, 24, 26]. Definitive surgical correction involves division and closure of the TEF in conjunction with airway restoration using a muscle flap interposition based on the defect's size and absence of airway stenosis [1, 12, 27, 28]. Differences in single vs. double-layer closure techniques and in the tissue used to close the defects have been reported; intercostal muscles and latissimus dorsi muscle flaps are the most commonly used [1, 12, 27, 28]. Due to the complexity and associated comorbidities, patients with acquired TEFs often receive stenting and surgical repair. However, surgical management for tracheal and esophageal defects remains controversial [2, 3, 12, 27, 28]. Stent placement has been shown to prevent aspiration pneumonia, and often, oral intake can be resumed after complete surgical closure of the fistula. However, most patients require nutritional support via gastrostomy, jejunostomy, or parenteral nutrition [3, 18, 22]. Furthermore, there are reported complications of endoscopic stenting, the most common being stent migration, bleeding, perforation, and, paradoxically, the formation of new TEFs [3, 18, 22]. Of the 31 individual cases of fistula reviewed, 32.3% were secondary to surgery or stenting (Table 1). Although considered a definitive treatment, fistula recurrence often complicates surgical repair, and can have an operative mortality rate reported as high as 11% from post-op emphysema, pneumonia, and hemorrhage [3, 26–28].

Overall, TEF should be suspected in patients with known risk factors or symptoms, such as recurrent bronchitis or pneumonia, or persistent coughing following nutritional intake. Management by a multidisciplinary team is essential and includes imaging and endoscopic findings for diagnosis, histologic analysis for differentiation between malignant and benign entities, evaluation of infectious etiologies and appropriate treatments for optimal outcomes. Fungal or bacterial infections causing benign TEF, while uncommon but not rare, need to be considered in diagnosis and treated quickly and appropriately for optimal outcomes.

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Contributions: The authors confirm contribution to the paper as follows:

Study conception and design: AMD.

Data collection: AT and RR.

Analysis and interpretation of results: CMGS, DPS, PK, AMD.

Draft manuscript preparation: AT, RR, OC.

Editing manuscript: CMGS, DPS, PK, AMD.

Illustration: OC.

All authors reviewed the results and approved the final version of the manuscript.

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