


CLINICAL GUIDELINE

Chinese expert consensus on diagnosis and management of acquired respiratory-digestive tract fistulas

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Abstract

Acquired respiratory-digestive tract fistulas occur with abnormal communication between the airways and digestive tract, causing the interflow of gas and liquid. Despite advances in surgical methods and the development of multimodal therapy in recent years, patients with acquired respiratory-digestive tract fistulas continue to exhibit unfavorable clinical outcomes. Therefore, in order to guide clinical practice in China, the Respiratory and Cancer Intervention Alliance of the Beijing Health Promotion Association organized a group of experienced experts in the field to develop this consensus document. Based on a study of clinical application and expert experience in the diagnosis and management of acquired respiratory-digestive tract fistulas at home and abroad, an Expert Consensus was developed. The panelists recruited comprised experts in pulmonology, oncology, thoracic surgery, interventional radiology, and gastroenterology. PubMed, Chinese Biology Abstract, Chinese Academic Journal, and Wanfang databases were used to identify relevant articles. The guidelines address etiology, classification, pathogenesis, diagnosis and management of acquired respiratory-digestive tract fistulas. The statements on treatment focus on the indications for different procedures, technical aspects, and preprocedural, post-procedural and complication management. The proposed guidelines for the diagnosis and

management of acquired respiratory-digestive tract fistulas are the first to be published by Chinese experts. These guidelines provide an in-depth review of the current evidence and standard of diagnosis and management.

Introduction

Airway fistulas occur with a loss of airway wall integrity and fistula formation and are classified as congenital or acquired. Current consensus focuses on acquired airway fistulas, which can be divided into aerodigestive and airway mediastinal fistulas. Acquired respiratory-digestive tract fistulas occur with abnormal communication between the airways and the digestive tract, causing the interflow of gas and liquid. Acquired respiratory-digestive tract fistulas are a morbid condition resulting in recurrent aspiration pneumonia, malnutrition, respiratory failure, and death. More than 90% of patients die of pulmonary infection in days to weeks if left untreated. Acquired respiratory-digestive tract fistulas are a critical illness concerning pulmonologists, interventional radiologists, thoracic surgeons, gastroenterologists, and oncologists. In recent years, advancements in various techniques of endoscopic and gastroscopic closure of fistulas have played an important and positive role in improving the quality of life and prolonging the survival of these patients. However, the current evidence-based data of acquired respiratory-digestive tract fistula is limited, mainly derived from case reports or series of case studies. Clinical diagnosis and treatment guidelines and consensus are lacking. In order to standardize the diagnosis and treatment of acquired respiratory-digestive tract fistulas in China, the Respiratory and Cancer Intervention Alliance of the Beijing Health Promotion Association invited experts from relevant fields to form a committee to draft a new consensus. PubMed, Chinese Biology Abstract, Chinese Academic Journal, and Wanfang databases were used to identify relevant articles. Disagreements were resolved by consensus. This consensus is based on principles of evidence-based medicine and international norms, combined with operability in clinical practice and new research data. Expert opinion was divided into 1–5 grades: grade 1, defined as complete agreement; grade 2 as agreement, opinions with reservations; grade 3 as opinions undecided; grade 4 as disagreement; and grade 5 as complete disagreement. Opinions scored grade 2–5 required reasons and suggestions as to how to improve the statement. When grade 1 and 2 opinions surpassed 80%, consensus was reached.

Etiology of acquired respiratory-digestive tract fistulas

Benign fistulas are attributable to many factors, including: blunt chest trauma; severe chemical esophageal burn;

tuberculosis involving the lung, trachea, bronchus, and mediastinal lymph nodes; esophageal perforations; tracheal intubation; esophageal surgery; radiotherapy after surgery; esophageal stents; trachea/bronchial syphilis; and other non-specific infection.^{1,2} Malignant fistulas are more common, often secondary to esophageal, mediastinal, or pulmonary malignancies. It is estimated that over 70% of all cases of malignant fistulas occur in patients with advanced esophageal cancer. Esophagorespiratory fistulas (ERF) develop in 0.2% to 5% of patients with esophageal cancer³ and in 1% of patients with lung cancer.^{4,5} Other etiologies of malignant fistulas include thyroid cancers and other neoplasms metastasized to the airway.

Classification and pathogenesis of acquired respiratory-digestive tract fistulas

Esophagorespiratory fistula (ERF)

Esophagorespiratory fistulas occur as a result of a variety of benign and malignant causes leading to the airway and adjacent esophageal rupture to form a pathological communication.^{1,6,7} ERFs are associated with high mortality, short survival, and poor quality of life.^{1,6,7} Fistulas develop in the trachea and bilateral main bronchi below the larynx. The most common location is between the middle esophagus and the left main bronchus. The etiology of fistulas can be divided into two categories: benign and malignant. Benign ERFs are mainly caused by surgery; esophageal stent placement; tracheal injury (tracheal intubation); infectious disease (such as tuberculosis, syphilis, fungal infection); and trauma. Advanced esophageal cancer invades the entire wall of the esophagus as the anterior walls of the upper and middle third esophagus are adjacent to the trachea and the posterior wall of the left main bronchus.^{7,8} Airway invasion and tumor growth cause ischemic necrosis of tissues and form fistulas. Radiation therapy not only kills tumor cells, but also inhibits the regeneration of normal esophageal tissue, resulting in tumor necrosis and the low ability of normal tissue to repair. It can lead to fibrosis and sclerosis of the esophagus, and decrease the functions of contraction and relaxation. These factors contribute to fistula formation. Systemic or local arterial infusion chemotherapy leading to necrosis and absorption of tumor tissue and regeneration injury to normal tissue also

contribute to the formation of fistulas. Dumbbell and horn shaped stents are often used to treat esophageal stricture in advanced esophageal cancer patients. Both ends of the stent exert great pressure or shear force on the esophagus wall, which reduces the blood supply to the esophagus, especially the anterior wall. When anastomotic stoma (upper arch and neck) tumors recur, the stents inserted stimulate the curved wall of the esophagus and trachea and the resulting friction leads to tissue necrosis and fistula formation.

Thoracostomach-airway fistula

Gastroesophageal supra-arch or cervical anastomosis is performed to place the stomach in the thoracic cavity or the posterior mediastinal esophagus bed. The stomach and airway form a new adjacent relationship. Thoracostomach-airway fistulas occur with abnormal communication between the stomach and the trachea or bronchus, which is the most serious and life-threatening complication of esophagogastrostomy for esophageal cancer.^{9,10} Factors related to the formation of thoraco stomach-airway fistulas include: (i) radiotherapy: the therapeutic and tolerance dose of esophageal radiotherapy is 60~70 Gy, while the stomach tolerance dose is approximately 30~40 Gy (the thoracic stomach located in the esophageal bed area is prone to radiation ulcers, gastric wall necrosis, perforation, and airway injury); (ii) gastric acid chemical stimulation and gastric juice digestive enzymes result in the local corrosion and perforation of the stomach; (iii) lung infection and mediastinal inflammation; (iv) recurrence and invasion of tumors; (v) poor suturing and tissue ischemia; (vi) chemotherapy; and (vii) malnutrition.

Esophageal anastomotic airway fistula

Esophageal anastomotic airway fistulas occur with abnormal communication between anastomotic stoma and airway. Fistulas are located in the special area where anastomotic stoma are located, and the upper and lower sides of the esophagus and wide stomach cavity, respectively. High dose radiation therapy and tumor recurrence in anastomotic stoma directly invade the airway after resection and anastomosis of esophageal carcinoma, leading to anastomotic leakage. Anastomotic stricture dilatation treatment and infection of anastomotic stoma also contribute to anastomotic leakage.

Esophagoalveolar fistula

“Esophagorespiratory fistula” is often used to describe all fistulas occurring between the esophagus and airway.

In fact, 50~60% of patients develop fistulas between the esophagus and trachea, while 37~40% develop fistulas between the esophagus and bronchus. A small number of patients develop esophagoalveolar fistulas.^{4,11,12} Studies have shown that esophagopulmonary fistulas mainly result from esophageal and bronchial cancer. Radiation and chemotherapy injure the mediastinum, pleura, and lung tissue and promote the formation of esophagopleural alveolar fistulas. All patients with esophagoalveolar fistulas develop aspiration pneumonia. Lung inflammation or abscess is observed in 79% of patients. Esophageal stenting is the main treatment procedure for patients with esophagoalveolar fistula. Although stent placement will reduce the range of pulmonary abscess, drainage of the abscess should be considered, as inserting a stent reduces access to the abscess cavity.

Diagnosis

A diagnosis of acquired respiratory-digestive tract fistula can be complex and requires careful examination. Diagnosis is based on clinical symptoms, imaging examination, and endoscopic findings.

Clinical symptoms

The typical clinical symptoms of acquired respiratory-digestive tract fistula are coughing associated with food intake, coupled with persistent and progressive dysphagia and dyspnea. Some patients present with a “burn-like cough supine position syndrome.” Scorched-like acute irritating coughing occurs and is aggravated in the supine position, while symptoms are relieved or disappear while in a sitting position. Most patients develop a large volume of viscous, bloody, or purulent sputum. Tracheobronchial gastric fistulas are more serious than ERF. Fasting reduces food entry into the airway, but cannot prevent digestive fluid, such as gastric juice and bile, from entering the airway through the fistula. The digestive effects of increased gastric juice often aggravate a fistula, causing it to grow in the short term. Coughing and pulmonary inflammation always occur, even during fasting. Inflammation is generally serious. Chemical inflammation can occur in early stages, while inflammation in late stage is often associated with bacteria and fungi. Patients are prone to developing respiratory dysfunction and failure because a large amount of inhaled gas enters the stomach cavity through the large fistula. If not dealt with in time, the patient will die in a short period. The symptoms of esophageal anastomotic airway fistula are similar to those of thoracogastric fistula, but are generally milder.

Imaging examination

X-ray radiography of the esophagus

X-ray radiography of the esophagus is of great value and 40% diamine is used as a contrast agent (iodized water contrast). Oppressing the upper abdomen by hand may improve diagnosis. However, X-ray imaging is not the optimal choice, particularly for patients with giant fistulas, as aspiration can occur when the contrast medium is swallowed. It is difficult to accurately assess the location, shape, length, and diameter of fistulas because of violent coughing. Angiography does not always reveal small fistulas. Barium sulfate should not be used during angiography because barium may result in recurrent pneumonia as a result of foreign body deposition. Oral esophagography or gastrography is recommended to avoid the blurring of images caused by violent coughing and the large volume of bacteria flushing during swallowing. A catheter is inserted into the predetermined fistula under imaging, 3 mL 40% iodine water contrast agent is injected through the catheter to the suspected esophageal fistula, and 5 mL contrast agent is injected into the suspected gastric fistula.

Computed tomography and magnetic resonance imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) are very important and useful modalities to assess the severity of acquired respiratory-digestive tract fistula and pneumonia, as well as the relationship between the fistula and the adjacent tissue to plan stent placement. For airway stenting, reconstructed CT images are very useful for measuring the distance between the fistula and a carina or vocal cord to determine optimal stent length.

Endoscopy (bronchoscopy and esophagoscopy)

Bronchoscopy is the most effective method to identify and locate fistulas in the trachea or bronchus. Detection of a fistula is easier if the patient sucks in any sections in their airway. The application of oral ethylene blue before bronchoscopy, followed by a check for bubbles leaking from the airway, can help to identify small fistulas. Combined with esophagography, gastroscopy is used to confirm the diagnosis. Gastroscopy not only allows direct visualization of the mucous membrane and tissue surrounding the fistula but also permits a biopsy to determine etiology and treatment. Gastroscopy is useful to monitor the healing of a fistula after stent placement.

Treatment

Surgery

Surgery should be performed for benign acquired respiratory-digestive tract fistulas to remove fistulas and pathogenic tissue if the clinical condition permits.¹³ Lobectomy or pneumonectomy is feasible to surgically remove the lung tissue with irreversible lesions, and esophageal diverticulum associated with fistula. A two-layer suture should be used to close the trachea, bronchus, and esophagus defects. Tissues, including the pleura flap, muscle flap, pericardium fat, or diaphragm flap, can be inserted between the esophagus and trachea to reduce fistula recurrence. In cases of a giant airway defect, it is feasible to transplant an airway substitute. Many patients with malignant fistulas are not eligible for surgery because of advanced cancer and poor physical condition.^{14,15}

Stent therapeutic interventions

Interventional therapy under the guidance of a bronchoscope, gastroscopy, and imaging is the mainstay of treatment for patients with acquired respiratory-digestive tract fistulas who are poor surgical candidates. It alleviates symptoms and significantly improves quality of life. The most common interventional therapies used are airway and or gastrointestinal stent placement,^{7,10,16–21} drug injection via endoscopy, cauterization, and metal clips. The ideal stent to treat fistula will completely occlude the communication between the gastrointestinal tract and airway, is well anchored, is easy to insert and remove, is not prone to migrate, and does not exert excessive radial pressure. Retrievable stents can be placed for benign fistulas, while long-term stents are required for malignant fistulas.

Airway stents

Current stents can be divided into several broad categories, including tube stents that are made of metal and silicon. Stents may prevent ongoing interflow of gas and liquid between the digestive tract and airway, as well as improve patient quality of life. Stents used include Ni-Ti alloy stents (Nanjing Microtech, Nanjing China), Z-shaped metal stents (Sigma Medical Apparatus, Huaian, Jiangsu, China), and Ultraflex stents (Boston Scientific Corporation, Boston, MA, USA).

Individualized design of stents

A tube stent can be used when the interval between the fistula orifice and normal lumen is greater than 10 mm. Bifurcation stents (Y or L shape) can be used when the

fistula orifice is close to the carina (locations II, III, IV, and V) or when there are not enough fixed points surrounding the upper and lower lumen of the fistula.²⁰ We propose eight zones of the central airway to classify various fistula locations in this consensus: location I, upper third trachea; location II, middle third trachea; location III, lower third trachea; location IV, trachea carina; location V, right main bronchus; location VI, right bronchus medium; location VII, proximal of left main bronchus; and location VIII, distal of left main bronchus (Fig 1).

The length of a stent should extend more than 20 mm beyond the range of lesions. The extension length of the Ni-Ti memory alloy stent under compression should be included in the total length. For a large fistula, the stent should cover the fistula by more than 20 mm. A determination of stent diameter should be based on the upper and lower airway diameters and the degree of stenosis of the fistula. In general, the stent diameter is 10~20% larger than that of airway or equal to the anteroposterior diameter of the airway. However, if the lumen near the fistula is obviously narrow, the stent should form a dumbbell, flashlight or tube shape. The airway length is measured under direct bronchoscopic vision. The parameter can be more accurately calculated using the positioning of a ruler or biopsy forceps. It can also be obtained from a CT scan. The most accurate method is to measure the airway diameter on the fat window of thin layer CT at a deep inspiratory phase. The value needs to be converted according to Pythagorean law formula when the oblique plane of the airway is present on CT scan.

Stent placement procedure

Straight tube metal airway stents (I-shaped) are placed via flexible bronchoscopy. Y-shaped stents are placed via rigid

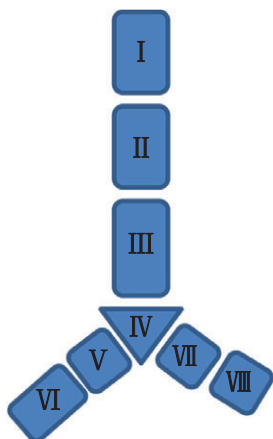


Figure 1 Proposed central airway zones to classify various fistula locations.

bronchoscopy. Any type of stents can be placed under X-ray fluoroscopy. A metal stent delivery kit is composed of an inner tube (stent-loaded), outer sheath, and pusher, namely the “three tube placement method.” The stent position is verified by positioning the ruler during deployment. Silicone stents are placed via rigid bronchoscopy. In rigid bronchoscopy, after applying general anesthesia, different calibers are inserted through the mouth according to the placement bracket model, and the silicone stent is then placed. Chest radiographs should be performed after placement to detect complications, including stent migration, pneumothorax, and mediastinal emphysema. Bronchoscopy should be performed regularly to dynamically monitor stent position. Complications should be dealt with in a timely manner.

Esophageal stents

Material selection

Esophageal metal stents (Boston Scientific Corporation and Cook Endoscopy, Boston, MA, USA; S & G Biotech and Taewoong, Seoul, Korea), Ni-Ti memory alloy stents (Minimal Invasive Company, Nanjing, China), and Z-type stainless steel stents (Sigma) are commonly used in clinic practice.¹⁶ Esophageal metal stents can be classified as fully or partially covered. Fully expandable esophageal covered metal stents with a mushroom head at both ends are widely used. These can effectively seal the fistula, and prevent food and gastric liquid from contacting the fistula and entering the airway. This also reduces the rate of lung infection and fistula growth, prevents tumor and granulation tissue from occluding the stent cavity, and reduces the incidence of stenosis after stent placement.

Individualized design of esophageal stents

The length of the stent should be more than 5 cm longer than the fistula. The upper edge of the stent should be more than 2 cm above the upper edge of the fistula. Stent diameter is 17~20 mm. For patients with a history of esophageal radiotherapy, a stent 14~16 mm in diameter should be chosen, and a 15~17 mm stent should be placed around the entrance of the esophagus.

Design of digestive stents for esophageal anastomotic airway fistula: Segmental full covered esophageal and segmental mushroom type fully covered stents placed in gastrointestinal tracts should not be too large. Part of the stent placed in the esophagus should be designed similar to the esophageal stent. The other part placed in the thoracic stomach should be designed in a large bellmouth shape to reduce side leakage of gastric contents entering the fistula along the external surface of the stent and the stomach

wall. Moreover, an anti-reflux valve may be attached to the lower end of the stent to reduce reflux of the thoracic stomach contents. If possible, it is best to place airway stents simultaneously.

Stent placement procedure

X-ray guided placement method

The advantages of using an X-ray to guide placement are that the position of the guide wire can be accurately judged, whether the lesion segment is passed or not; medical perforation is reduced; and the release process of the stent can be dynamically monitored, particularly the release of the lower edge of the stent.^{22,23} The efficacy of fistula closure can be evaluated by angiography after stent placement. Sole X-ray guidance cannot be used to view esophageal lesions and fistulas directly and effectively to detect complications, such as bleeding and perforation, during stent placement. Once complications occur they cannot be dealt with in time.

Direct vision via gastroscopy

The main advantages of direct vision via gastroscopy are the direct view, ease of operation, high success rate, avoidance of X-ray (radiation) damage, timely treatment of intraoperative bleeding, safety of the implantation process, and timely adjustment of the position of the stent under direct vision. However, the positioning accuracy is poor when stents are placed directly under gastroscopy. The fistula closure, stent opening, and displacement should be evaluated via esophageal CT or endoscopy one week after placement, and then every one to two months after stent implantation according to the patient's condition.¹⁶

Choice of stents for different acquired respiratory-digestive tract fistula/ERF

Esophageal stent alone

In malignant and benign ERF patients, an esophageal metallic stent can be used to close the fistula without operative indications. An esophageal stent alone is recommended in patients with esophageal stenosis, regardless of mild airway stenosis. The incidence of migration in patients with ERF without obvious esophageal stenosis that have undergone esophageal stent placement alone is high. A combination of esophageal uncovered and covered metal stent placement is recommended. The former exerts a fixed effect, while the latter closes the fistula. Esophageal stents are only suitable for ERF patients with fistulas located less than 21 cm from the incisor teeth. Because the upper

esophageal sphincter is comprised of striated muscle and its position is high, pain and foreign body sensation are common and obvious in patients after stent placement. However, with improvements to the covered metal stent and digestive endoscopy, upper esophageal ERF can also be treated by stent placement. Stent placement is still the indication for fistulas located in the upper zone when the upper edge of the stent does not surpass the first physiological stricture of the esophagus. The long-term effect is satisfactory and does not increase the rate of complications.^{24–26} Esophageal metal stents are generally not suitable for thoracogastric and most anastomotic fistulas.

Airway stent alone

Airway stent placement can be considered in a population with ERF located in the upper cervical esophagus when the esophageal stent is difficult to place after gastroscopy and imaging evaluation. If the esophageal lumen distal to the fistula is completely obstructed, the esophageal stent cannot be inserted if the guide-wire cannot be inserted into the gastric cavity. Esophageal stent placement may lead to esophageal rupture. Airway stents can relieve stenosis and also occlude the fistula orifice in patients with moderate to severe airway stenosis but without or with slight esophageal stenosis.

Combined placement of airway and esophageal stents

Esophageal stent placement alone may be insufficient for palliation. Studies have shown that the fistula is not completely closed after multiple esophageal stent placements. Tracheal stents should be considered in these cases. Esophageal stents may be removed if necessary.²⁷ In cases of moderate and severe esophageal and central airway stenosis, single stent placement may not be sufficient to relieve symptoms. A combination of esophageal and tracheal stents may be considered to relieve esophageal and airway stenosis.²⁸ In these cases, airway stent placement should precede esophageal stent placement. If the esophageal stent is placed first, the stent may compromise the airway, aggravate airway stenosis and dyspnea, and even threaten life. Double stents carry the risk of pressure necrosis of interposed tissue caused by mechanical friction, thereby leading to potential extension of the fistula over time and fatal bleeding. Therefore, a combination of esophageal and airway metal stent placement requires comprehensive evaluation of ERF patients. The size of the fistula and its relationship to blood vessels should be noted. Stent should be placed with caution when the fistula is too close

to large vessels. Airway stents interact with esophageal stents to inhibit migration.

Airway thoracogastric fistula

Because airway stents (mostly Y-shaped) are placed through the esophagogastric pathway and cannot close a fistula located in the wide stomach body, they must be placed alone. However, esophageal stents are required when the fistula orifice is located in the tubular stomach.

Esophageal anastomotic airway fistula

An airway stent should be placed first, and an esophageal stent specially designed if necessary. Because of the position of esophageal anastomotic airway fistulas, esophageal stents cannot completely occlude the fistula and can only reduce food and secretions flowing into the airway.

Efficacy evaluation

Most acquired aerodigestive fistulas are difficult to treat and cannot be cured by surgery and drugs. Airway and alimentary tract stent placement is the most effective treatment for acquired respiratory-digestive tract fistulas, which can be occluded by physical methods, thereby preventing food and secretions from entering the respiratory tract through the fistula, controlling pneumonia, and preventing respiratory gases from entering the digestive tract. Stent placement also relieves coexisting airway or esophageal stenosis. Clinical practice has proven that airway and esophageal stent placements are less invasive, are associated with fewer complications, and yield a definite effect. The procedure is not affected by the physical condition or age of the patient. The stent can be removed at any time, and has become the most feasible and commonly used method for the palliative treatment of acquired respiratory-digestive tract fistula.

Until now, no criterion to evaluate the efficacy of treatment of airway fistula has been available. Wang *et al.* established a standard evaluation to determine the efficacy of stent fistula closure based on experience from multiple centers in China: complete remission (CR) is defined as the seal of the fistula and complete relief of clinical symptoms (such as drinking water choking, fever, etc.) for one month; clinical complete remission (cCR) is defined as the fistula having been sealed but completely occluded by stents, and complete relief of clinical symptoms for one month; partial remission (PR) is defined when the fistula is not closed and is partially occluded by a stent, and the clinical symptoms are partially relieved; and ineffective (NR) is defined when the fistula is not closed, not occluded by a stent, and the clinical symptoms are not

relieved.²¹ Whether the stent placement can successfully close the fistula is closely related to the individual design of the stent. Only by designing individualized stents based on the location, nature, airway, and esophageal characteristics of the fistula can they be occluded to the maximum extent, control infection, and allow the patient to resume oral intake. According to the central airway classification scheme proposed by Wang *et al.*, Y-shaped airway stents are used for patients with fistulas in locations II, III, V, and VII. I-shaped airway and esophageal stents are adopted for patients with fistulas in locations I, II, and VIII. The small Y-shaped stent is designed for patients with fistulas in locations VI and VIII. The diameters of 52 fistula orifices in 48 ERF patients were reported as 0.3–7.0 cm. Most of these fistula orifices were located at the middle and lower third trachea (locations II and III) and bilateral bronchial orifice (locations VI and VII). Covered Z-stents were used in 52 cases, Y-shaped in 36 cases, L-shaped in 8 cases, and I-shaped in 8 cases. Covered esophageal stents were placed in 28 cases. Among these, CR, cCR, PR, and NR were 4.0%, 68%, 18%, and 10.0% respectively. ERF can be effectively occluded using the appropriate shape and type of trachea and/or esophagus covered metal stents.²¹

However, there is insufficient evidence regarding treatment for benign ERF. Retrospective studies have revealed that the clinical success rate of various interventions is close to 95%, and the rate of continuous clinical remission is > 90%. Recently, the European Society of Gastrointestinal Endoscopy (ESGE) suggested that stent placement should be considered for benign ERF, but no specific type of stent was recommended. The optimal time for stent placement should be determined according to each individual case. Self-expandable covered metallic stents can be used to treat benign ERF and other endoscopic treatments, such as over-the-scope-clips (OTSC), can also be adopted. Limited clinical data is available on the use of biodegradable stents for benign ERF. Small sample studies have shown that biodegradable stents can achieve good efficacy. Self-expanding covered or uncovered metal stents have become the mainstay of palliative therapy for ERF since their introduction in the early 1990s. Retrospective studies have shown that the successful rate of closure of fistula in patients with ERF treated by self-expandable metal stent is 70–100%.^{8,16,29–32} Recently, guidelines released by ESGE recommend a self-expandable metal stent as the optimal treatment for sealing malignant ERF. However, the optimal time for stent placement is still uncertain, and should be individualized.¹⁷ When ERF caused by esophageal cancer is accompanied by esophageal stenosis without or with mild tracheal stenosis, the effect of self-expandable metal esophageal stents is immediate, but problems such as stent migration and remission can occur after placement.

The rate of incomplete closure of fistula has been reported as approximately 12% in patients who received esophageal stent placement within one week, because of residual space between the proximal edge of the stent and esophagus wall.⁷ Stent replacement or other plugging techniques are performed to eliminate the space.^{7,30,33,34} The “funnel phenomenon” exerts a negative curative effect. In addition, tracheal stent placement alone should be considered when tracheal stenosis exists. Both esophageal and tracheal stents should be placed in patients with moderate to severe esophagus and trachea stenosis or large fistulas.^{7,31,35} ESGE also recommend that double stent placement is considered when the fistula cannot be closed by esophageal or tracheal stent placement alone.¹⁷

Silicone stents offer many advantages, including robust design, durability, a reliable plugging effect, and are less influenced by coughing.¹⁸ On the premise that the stents fit well with the wall around the fistula, silicone stents can obtain a more satisfactory sealing effect and a longer plugging time than metal stents. Silicone stents should be properly modified according to the location of the fistula. Silicone stents can be directly placed when airway fistulas are located in the tracheal membrane; for fistulas located in the side wall of the airway, it is necessary to remove the studs in the side wall of the stent before placement. However, because of poor conformability and the presence of the studs, silicone stents cannot closely anchor to the wall around the fistula, and placement is difficult. A risk of the fistula expanding also exists, thus the operator requires superior technical expertise. Silicone stents are not suitable for the treatment of tracheobronchial fistulas, including those with stents not well aligned with the wall around the fistula because of poor conformability or diameter limitation, and those for which corresponding rigid endoscopy is difficult to insert or fails to insert into the distal end of the fistula. A study reported short-term efficacy of silicone stents for the treatment of 31 cases with acquired aerodigestive fistula. Silicone stents were successfully placed in all patients: 41.4% achieved CR and 41.9% achieved PR, and the overall rate of symptom remission was 90.3%.¹⁸ In addition, 16 patients with airway thoracogastric fistula were treated with silicone stents in China: CR was 25%, PR was 56.3%, and NR 18.7. The effect was similar to that of placing a metal stent.³⁶

Long-term survival after stent placement for acquired aerodigestive fistula is not conclusive. Survival in patients with malignant ERF treated with esophageal and/or airway stent placement depends on the extent of fistula closure. If the fistula is effectively closed and pulmonary infection is controlled, quality of life and survival will be significantly improved. A control study showed that the quality of life of malignant ERF patients with stent placement was significantly better than that of control and gastrostomy

groups,^{17,37} especially for improving dyspnea, dysphagia, dietary problems, dry mouth, cough, and excessive secretion of saliva. A series of case studies reported a mean survival rate in a stent placement group of 3.4 months, which was significantly higher than that of enterostomy and nutrition support alone groups.^{17,32}

Stent-related complications

Airway stent-related complications

The major complications of metal stents include coughing, sputum retention, incomplete closure of fistula, stent displacement or prolapse, granulation tissue proliferation at both ends of the stent, halitosis, metal fatigue, stent rupture, respiratory tract infection, tracheobronchial perforation, and massive hemorrhage. The major complications related to silicone stents include coughing, migration, obstruction of fistula, formation of granuloma, and pulmonary infection.^{18,36} These complications are generally non-fatal and can be treated.

Esophageal stent-related complications

The incidence of procedure-related complications ranges from 0–27%. The related mortality rate ranges from 0–12%. The major complications related to esophageal stent include stent migration, perforation or fistula formation, granulomatous obstruction, and tumor ingrowth and overgrowth.^{30,31,35,38} The recurrence of symptoms indicates the reopening of a fistula, which is difficult to treat. Reopening of the fistula is reported at a rate of 10–30% of ERF patients after initial success of one month.⁶ Stent adjustment or re-placement via endoscopy will resolve problems of incomplete closure of the fistula, and stent obstruction and migration.

Postoperative management and follow-up

Postoperative management and regular follow-up should be performed regardless of whether an airway or esophageal stent is placed. Endoscopy should be performed at least once within a week after placement. Any complications should be dealt with in a timely manner. Secretion retention often occurs two weeks after airway stenting. Alkaline liquid inhaled by ultrasonic atomization at least four to six times per day combined with intravenous fluid is employed to humidify sputum. Bronchoscopy should be performed once a week. Granulomas often appear after one month. Bronchoscopy should be performed monthly within three months. Rupture of the membrane and symptoms of choking cough often reappear after six months in

some patients after covered metal stent placement, indicating that the stent needs to be changed in time. Esophageal stents can often migrate in the early phase and thus should be closely observed. Granulation often appears after three months at both ends of the stent, and also needs to be dealt with in a timely manner.

Other interventional therapy

Drug injection via endoscopy

Sclerosing agents or stem cells can be injected into the tissue surrounding the fistula. Petrella *et al.* demonstrated that bone marrow mesenchymal stem cells effectively sealed off bronchopleural fistula in an animal model.³⁹ In another study, a patient who developed a right main bronchopleural fistula (approximately 3 mm) after right pneumonectomy was treated with an injection of bone marrow mesenchymal stem cells.⁴⁰ After isolation and culture of the bone marrow mesenchymal stem cells, 10 million stem cells were injected via bronchoscopy around the fistula. CT and bronchoscopy examination showed that the fistula had completely closed after 60 days. The biopsy tissue at the fistula site showed airway epithelial cells in the upper layer of the lamina propria proliferate, while smooth muscle cells were decreased and replaced by fibroblasts. Immunohistochemical staining showed positive p40 and DNP63 phenotypes, indicating that basal cells differentiate into squamous epithelium and show a good repair effect.

Another study demonstrated that autologous adipose-derived stem cells were endoscopically injected into the de-epithelialized area and fistulous tract of patients with bronchopleural fistula.⁴¹ Three-year follow-up revealed successful and maintained fistula closure, no treatment-related adverse events, and no tumor recurrence. Adipose stem cells were also successfully used to treat a patient with bronchial mediastinal fistula.⁴²

Interventional therapy via digestive endoscopy

Interventional therapy via digestive endoscopy consists of endoscopic anastomosis clip and endoscopic OTSC anastomosis systems to close a fistula. A pointed tooth type of OTSC is used to close small benign fistulas resulting from traumatic injury or foreign body.^{43,44} In 2008, the Ovesco Company from Germany introduced the OTSC anastomosis system, a new type of nickel-titanium alloy clamp, which closes larger amounts of tissue than the traditional endoscopic metal clamp, closing a full-thickness wall and exerting less tension to the surrounding tissue. The efficacy of OTSC for the closure of gastrointestinal fistulas is better than that of the endoscopic metal clip, but it is expensive

and thus is not yet widely used in clinical practice. The appropriate size of an anastomosis clamp should be selected according to the size of the fistula. Application of OTSC is relatively difficult because of the small esophageal lumen and fibrosis or necrosis of tissue surrounding the fistula, which may lead to the instability of anastomosis and exfoliation. Auxiliary equipment is employed to suction secretion. The edge tissue is completely pulled into the cap and the anastomosis clip is deployed. Although OTSC has been successfully used for ERF closure in several reports, there is limited evidence of the clinical application of ERF. There is also a lack of high quality data to indicate how to select the size and type of OTSC for different types of ERF. Metal clamping combined with argon plasma coagulation is also employed to treat ERF.

Other bronchoscopic approaches

Tracheal stent placement combined with cauterization via bronchoscopy and bio-clue instilling is used to treat small fistulas. However, the fistula will recanalize after one to two weeks as a result of the dissolution of biogel. Bio-clue is less commonly applied in clinical practice.⁴⁵

Conservative treatments

Conservative medical treatments are applied as basic treatment for poor surgical candidates with acquired respiratory-digestive tract fistula, and include anti-infective therapy to control pulmonary infection, intravenous nutrition, jejunostomy, and phlegm, as well as other symptomatic treatments. Gastric tubes should be placed for gastrointestinal decompression in patients with tracheo-thoracic and esophageal anastomotic airway fistulas to reduce the flow of acidic gastric juice into the airway. The main treatment options are listed as follows.

Anti-infective therapy

Once a fistula develops, the prognosis is often poor. Most patients die of respiratory tract infection and malnutrition within a month. A study from China reported that gram-negative bacteria and fungi are the main pathogens in lower respiratory tract infection of patients with ERF.⁴⁶

Nutrition support

Patients with ERF often suffer from severe malnutrition as a result of their inability to eat through the mouth and the stress and inflammatory responses caused by infection. Malnutrition leads to delayed healing or failure to heal and can lead to a significant increase in clinical complications.

Therefore, effective nutritional support is essential in the overall therapeutic strategy for ERF.^{47–49}

Comprehensive evaluation of nutritional status should be performed, including nutrition screening, anthropometry, blood index, body composition analysis, and metabolic determination. A nutrition treatment scheme, including nutrient support pathways and nutrient selection, should also be provided. In the early stage of a fistula, parenteral nutrition support should be provided when jejunal nutrition has not been established. Enteral nutrition should be administered early to meet daily nutritional requirements. Transnasal or percutaneous jejunal nutrition is recommended to avoid gastric reflux. It is recommended that a continuous micropump-controlled velocity pump be employed to pump enteral nutrition fluid gradually. Energy should be administered at 25–35 kcal/(kg•d). The adipose energy supply ratio should be appropriately increased according to the degree of patient stress, accounting for 40% to 50% of the non-protein energy. Protein should be supplied based on 1 g/(kg•d) and the target supply is 1.2 to 2 g/(kg•d). Is it recommended that whey protein be used to supplement protein when insufficient. Intact protein enteral nutrition is recommended when intestinal function is normal, while element enteral nutrition is recommended when intestinal function is poor. Nutritional supplements containing immunonutrients are recommended. Micronutrient supplements are recommended based on the monitoring results. Special attention should be paid to avoid the development of refeeding syndrome in the early nutritional support phase in patients with severe malnutrition. Phosphorus, potassium, calcium, magnesium and vitamin B1 levels should be monitored and supplemented as necessary. The effect of nutrition strategies should be regularly evaluated. Weight, blood electrolytes, liver and renal function, and body composition should be regularly monitored.

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