Endoscopic Management of Bronchopleural Fistulas

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Abstract

A bronchopleural fistula (BPF) is an abnormal communication between the airway and the pleural space. It most commonly occurs after pulmonary resection but may be a result of multiple benign and malignant diseases. Patients with BPFs may present with a variety of symptoms, but they typically include fatigue, cough, dyspnea, and/or purulent sputum. In the acute setting, symptoms may be life-threatening as a tension pneumothorax can develop. Bronchopleural fistulas may be treated surgically or semi-invasively using endoscopic techniques. Endoscopic therapies for closure of a BPF include various sealants and glues, one-way endobronchial valves, and airway stents to cover the defect. Although there is a general consensus that endoscopic therapies are safe and well tolerated in a majority of patients, there are no large series or randomized trials exploring specific therapies or patient outcomes. The choice of therapy (endoscopic vs. surgical) is highly dependent on individual patient situation and physician preference. These techniques are not mutually exclusive, and combination therapies should be explored.

Keywords

One-way endobronchial valves · Chest tube · Pulmonary resection · Pleural space · Central airway

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1 Introduction

A bronchopleural fistula (BPF) is an abnormal communication between a proximal airway, that is, a main stem, a lobar or a segmental bronchus, and the pleural space. It needs to be differentiated from an alveolar-pleural fistula (APF), which is a connection of the lung parenchyma distal to the segmental bronchi with the pleural cavity. If a BPF or a APF persists for more than 5 days after establishment of a chest tube drainage, it is also considered as persistent or prolonged air leak (PAL).

A bronchopleural fistula is most commonly seen after thoracic surgery; however, it can occur in many other benign and malignant diseases. Bronchopleural fistulas can be classified as either central (visibly seen as a hole in the large airways, such as a stump leak after surgery) or peripheral (non-visible if air leak is located in distal airways or on the visceral pleural surface). Diagnosis is challenging and often delayed. As a BPF represents a communication from the non-sterile airway to the sterile pleural space, it is critical to identify a fistula and initiate treatment in a timely fashion. Although surgical techniques have improved, mortality remains high even with successful operative intervention. Advances in therapeutic endoscopic techniques have provided an adjunct to traditional surgical procedures.

2 Etiologies

2.1 Nonsurgical Etiologies of Bronchopleural Fistula

A bronchopleural fistula can form in any situation where tissue necrosis and/or impaired mucosal healing after trauma or infection can occur. Necrotizing lung infections (bacterial, tubercular, fungal pneumonia, or abscess) or empyema can lead to BPF. The pooling of secretions and loss of tissue planes due to necrosis creates a poor healing environment and possible development of a fistula tract. Penetrating trauma to the visceral pleural surface (as seen with a gunshot wound, stabbing with a knife, or iatrogenic by a thoracentesis/biopsy needle) can lead to a pneumothorax with leakage of air through the puncture site into the pleural space. If the defect is small enough and the underlying lung parenchyma is not too diseased, the pleural surface heals and the defect closes. A persistent pneumothorax (>72 h) indicates that the defect is not closing and there is a continued communication between the airway and pleura. Rupture of lung tissue, whether spontaneous or related to underlying lung disease (bullae, COPD, ARDS, and pulmonary fibrosis), likewise can lead to a persistent defect in the visceral pleura and BPF formation.

Lung or airway malignancy with endobronchial involvement can lead to loss of airway integrity and fistula formation. Mediastinal malignancies such as lymphoma or thymoma can directly invade into the airway, which may lead to a fistula tract into the mediastinum or pleura. A dramatic response to treatment (either by radiation or chemotherapy) of a malignancy, which has a large bulk of tumor invading into the airway, can be problematic if the tumor "melts" away and no normal tissue is available to fill in the defect (Fig. 1). Esophageal malignancy with erosion into the airway typically leads to a tracheo- or bronchoesophageal fistula; however, once the integrity of the airway wall is compromised, a communication can form between the airway and the mediastinum or pleural space. Likewise, severe gastroesophageal reflux disease complicated by Barrett's esophagus or Boerhaave's syndrome may cause enough airway inflammation to create a fistulous tract. A comprehensive list of possible etiologies of a bronchopleural fistula can be found on Table 1.

2.2 Postoperative Bronchopleural Fistula

Surgery on the thorax, especially pulmonary resection, is the most common etiology of a bronchopleural fistula (BPF). The incidence is highly dependent on surgical technique, complexity of surgery, and experience of the surgeon. Postoperative bronchopleural fistula has been reported to occur in 1.5–28% of all pulmonary resections. Multiple surgical and nonsurgical risk factors have been associated with the development of postoperative BPF (Table 2). Surgical complexity and extensive dissection are important risk factors. Although postoperative BPF may be seen in 4.5–20% of pneumonectomies, this complication is seen in only about 0.5–1% of lobectomies. Right-sided surgery is an important risk factor for BPF formation. A 10-year review of surgical data demonstrated almost threefold higher risk of BPF after right pneumonectomy compared to left (13.2% vs. 5.0%, $p = 0.047$). A subsequent meta-analysis demonstrated BPF to be an independent risk factor for death after right pneumonectomy with a relative risk (RR) of 3.39 for death after right pneumonectomy. Right-sided operations are technically more complicated and more likely to involve extended dissection, hand-sewn closures, closed buttress, or intrapericardial dissection. Postoperatively, right-sided stumps also tend to pool secretions more, which can impair complete healing.

Pneumonectomy for benign lung disease is generally more likely to result in BPF than for cancer resection. This increased risk may be due to the commonly infectious indications, the higher likelihood of completion rather than primary pneumonectomy, and the fact that 37% of these cases are performed as nonelective procedures. In patients undergoing pulmonary resection for malignancy, a longer bronchial stump was an independent risk factor for BPF. A recent

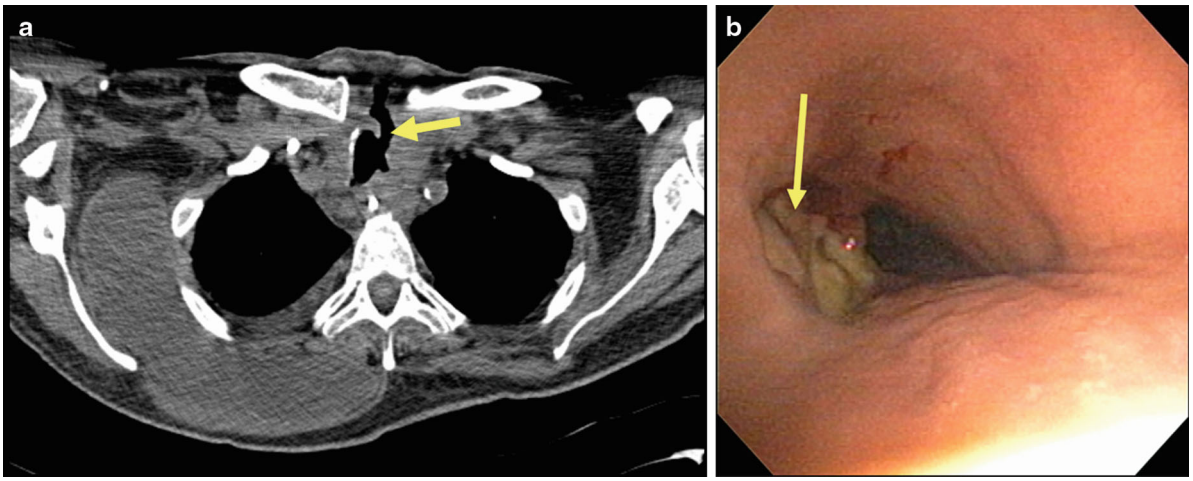

Fig. 1 Airway fistula developing as a result of treatment for lymphoma. (**a**) A 48-year-old man with B cell lymphoma who underwent chemotherapy and radiation. Lymphoma had eroded into the trachea, and after effective chemotherapy, large airway defect (*arrow*) was present. (**b**) Corresponding endoscopic view of tracheal wall defect

Table 1 Etiologies of bronchopleural fistula

Postoperatively after thoracic surgery
Necrotizing pulmonary infection
Tuberculosis
Haemophilus influenzae
Streptococcus viridans
Staphylococcus aureus
Pseudomonas aeruginosa
Klebsiella pneumoniae
Pneumococcus
Nonhemolytic streptococcus
Aspergillus
Histoplasma capsulatum
Lung disease or structural abnormalities
Pulmonary abscess rupture
Rupture of bullae or cyst
Persistent spontaneous pneumothorax or other parenchymal abnormalities
Recurrence at stump from prior resection
Residual tumor in resection margins
Broncholithiasis
ARDS
Malignancy (lung, thyroid, lymphoma, esophageal)
Advanced disease with tumor eroding into airway
Radiation and/or chemotherapy
Penetrating thoracic trauma
Postinterventional complication of
Percutaneous lung needle biopsy or thoracentesis
Tracheostomy
Bronchoscopy
Bougie intubation
Prolonged postoperative mechanical ventilation
Ventilator-induced barotrauma
Overzealous manual ventilation
Central line placement
Extrapulmonary diseases
Gastroesophageal reflux disease with Barrett's esophagus
Boerhaave's syndrome
Diabetes mellitus
Idiopathic

Table 2 Risk factors associated with increased risk of postoperative bronchopleural fistula

Surgical factors
Right-sided pulmonary resections (especially right pneumonectomy)
Excessive peribronchial or paratracheal dissection
Long bronchial stump/short distance from tumor to stump
Mediastinal lymph node dissection
High-dose preoperative radiation therapy
Residual/recurrent carcinoma/tumor at surgical stump
Large diameter bronchial stum (>25 mm)
Postoperative infection (pneumonia, abscess, empyema)
Previous ipsilateral thoracotomy
Bronchial artery damage due to excessive intraoperative free bronchi
Nonsurgical factors
Older age (>60 years)
Male gender
Diabetes mellitus
Hypoalbuminemia
Low nutritional status or poor wound healing
Heavy smoking
Chronic obstructive airway disease
Prolonged postoperative use of steroids
Preoperative respiratory failure
Cirrhosis
Haemophilus influenzae in sputum
Postoperative mechanical ventilation for >24 h

meta-analysis of 30 studies showed that neoadjuvant radiotherapy alone or as combination chemoradiotherapy, but not neoadjuvant chemotherapy alone, increased the risk of BPF significantly.

Patient factors including advanced age, male gender, diabetes mellitus, concurrent steroid use, hypoalbuminemia, cirrhosis, *Haemophilus influenzae* in sputum, residual tumor at stump, and postoperative mechanical ventilation for >24-h post-surgery have all been implicated in the development of a postoperative BPF.

3 Clinical Presentation

3.1 Postoperative Patient

Based on the time of onset, the modified Le Brigand classification categorizes BPF after pneumonectomy as follows: early (within 1–7 days post-surgery), intermediate (between 8 and 30 days post-surgery), and late (occurring more than 30 days post-surgery). Overall, bronchopleural fistulas are most commonly diagnosed between 8 and 12 days following surgery.

The presentation of an early bronchopleural fistula developing acutely (within hours to days) after surgery is fairly dramatic and in most cases due to surgical stump suturing or ischemic necrosis. It is heralded as the sudden onset of dyspnea, subcutaneous or mediastinal emphysema, cough with purulent sputum, or a life-threatening tension pneumothorax. Thoracic surgery patients invariably have a chest tube in the immediate postoperative period to avoid or immediately identify this complication. A continuous air leak or increase in the output of air in the waterseal chamber of a pleural fluid collection container should alert the physician to the possibility of a bronchopleural fistula. Bronchopleural fistulas identified within the first 4 days postoperative should return for re-exploration and closure of the stump leak if clinical situation allows.

The intermediate or late presentation for a bronchopleural fistula is less impressive and often associated with an infiltration of the growing tumor in the stump or chronic ischemia. Patients complain of fatigue, wasting, dyspnea, low-grade fevers, or productive cough. Hemoptysis or metalloptysis (coughing of surgical material) has been described. After pneumonectomy, there is an expected degree of and air and fluid present for at least a few weeks. The space is usually obliterated within 7 months. A major decrease in pleural effusion or dramatic change in the air–fluid pattern (increasing pneumothorax, changes in hydropneumothorax level, and new air–fluid level) after pulmonary resection should raise concern for a postoperative BPF. Depending on type of surgery and loculation(s) in the pleural space, subtle changes may not be readily visualized on a plain chest radiograph. In the chronic setting, bronchopleural fistulas typically occur as a result of chronic pleural space infection or fibrosis, usually in an immunocompromised patient. Reappearance of air in a previous obliterated space is an ominous sign for BPF.

3.2 Non-Postoperative Patient

The presentation of a BPF in the non-postoperative patient depends on the characteristics of the underlying disease. Most patients will have fever, persistent cough, thick and/or copious sputum production, and a pleural effusion with an air–fluid level. A patient with existing pneumonia or empyema, however, may already be exhibiting these symptoms leading to a delay in diagnosis. A non-resolving pneumonia, infiltrate, or effusion, especially in a patient with underlying lung disease, should warrant further investigation. In patients on mechanical ventilation, an abrupt and significant decrease in airway pressures should raise concerns for BPF formation. Hemoptysis may occur in malignancy-related fistulas, and cough and SOB during eating can be seen with esophageal to airway fistulas.

4 Diagnosis

Most patients with symptoms compatible with a BPF will initially be evaluated with a chest radiograph. Findings on radiographs may be nonspecific and include pneumothorax, subcutaneous emphysema, and/or pneumomediastinum. In a postoperative patient, a fluid collection adjacent to the stump may be identified. Strong indicators for a BPF are the appearance of new air-fluid planes, the development of a tension pneumothorax and decreasing air-fluid levels ≥2 cm, over time, indicating pleural fluid displacement. Although a computer tomography (CT) of the chest is much more sensitive at identifying abnormalities related to a BPF, it likely will not identify the location of the fistula itself. In a small study by Westcott and Volpe in 1995, in patients with clinical suspicion for BPF, the fistula site could be isolated on CT scans in only 50% of the patients. Figure 2 demonstrates the radiographic appearance of a BPF.

Bronchoscopy should be performed in all patients suspected of having a BPF. In large or central lesions, it may be possible to directly visualize the fistula opening. In the case of a suspected postoperative BPF, the stump should be closely examined. If stump dehiscence is not seen, saline should be instilled onto the stump. The presence of

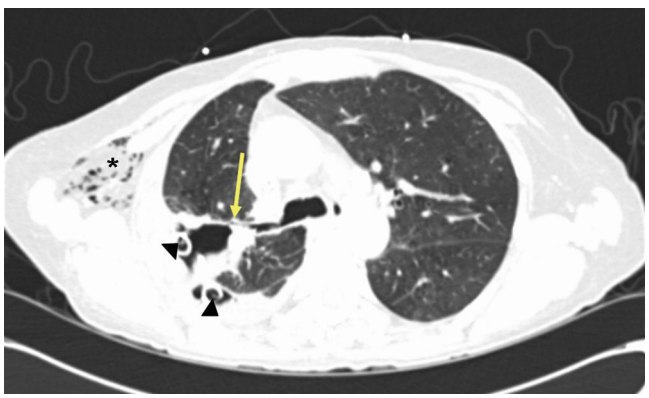

Fig. 2 CT appearance of BPF (*arrow*) in right upper lobe. Note chest tubes (*arrowhead*) and subcutaneous emphysema (*asterisk*) in this postoperative patient

continuous bubbling of saline from the stump indicates a fistula is present (Fig. 3). In the immediate postoperative patient, installation of methylene blue onto stump can be performed. Its presence in the chest tube output indicates a BPF is present. Also, retrograde administration of methylene blue into the thoracic drainage under bronchoscopic observation can be performed. It should be noted, however, that the presence of the dye may affect the in situ tissue discriminability if subsequent surgery is required.

If a fistula cannot be seen within the central airways, a bronchoscopy can still be helpful in determining the approximate location of a peripheral bronchopleural fistula. In patients with a chest tube, a balloon can be inserted via the working channel of the bronchoscope and inserted into the segment or subsegment of the airway with suspected fistula (Fig. 4). Once inflated, the balloon will occlude airflow through the fistula, and therefore, the air leak will decrease or disappear in the waterseal chamber of a pleural collection device. If the segment does not contain a fistula, inflation of the balloon will have no impact on the air leak. If even the general location of the fistula is unknown, a larger balloon can be inflated in the larger airways before proceeding to the segmental bronchi to provide the bronchoscopist with the general location of the fistula. In some cases, more than one airway may be contributing to a fistula, so multiple balloon inflations may be necessary to identify the culprit airways.

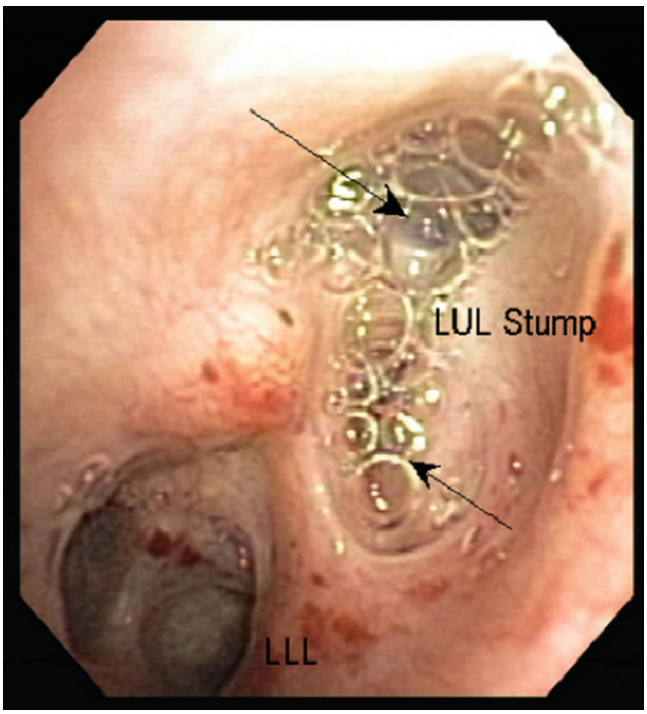

Fig. 3 A 70-year-old woman s/p LUL lobectomy with stump leak. Saline injected via flexible bronchoscope indicated continuous air bubbling (*arrows*) back through stump

A peripheral BPF can also be identified by a change in the pressure of the airway leading to the fistula. The Chartis System (Pulmonx, Redwood City, CA) is able to measure airflow and pressure in the airway distal to the bronchoscope (Fig. 5). It was originally designed to quantify collateral ventilation for endoscopic lung volume reduction. Once the bronchoscope is navigated to the target airway, a balloon catheter is inflated, and the airway is occluded. The tip of the catheter has a pressure sensor that provides measurement of airflow and pressure in the occluded airway (see Fig. 5 for details). As long as the airway is intact and there is adequate seal with the balloon, a small or no drop in pressure will occur with balloon inflation. If the pressure remains negative during both inspiration and expiration, a BPF is present. Capnography (measurement of exhaled carbon dioxide) can also be helpful in identifying the location of a fistula. A polyurethane catheter attached to a capnometer can be placed through the bronchoscope and inserted into sequential airways. During exhalation, carbon dioxide should be detected within the airway. The absence of an end tidal CO_2 tracing in a particular segment identifies the segment with the fistula as the carbon dioxide leaks out into the pleural space. Both airway pressure measurement and capnography are useful in identifying BPFs in patients without chest tubes or in situations where subtle changes in bubbling through the waterseal chamber occur when a balloon is occluding airflow.

Advanced imaging techniques may be helpful in the diagnosis of a bronchopleural fistula. Bronchography can be done if any of the abovementioned bronchoscopic techniques are inconclusive. In bronchography, 20–30 mL of a water-based

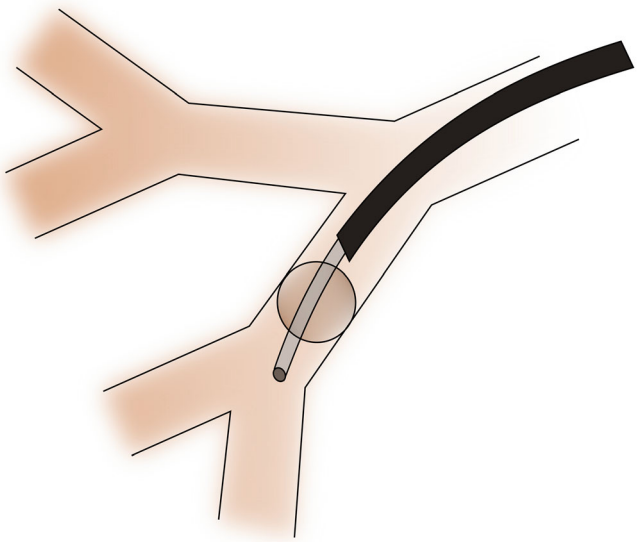

Fig. 4 Bronchoscopic localization of a peripheral BPF. Inflating a balloon within airway leading to a BPF will stop airflow into effected airway. This will either (1) slow or stop the air leak in water seal chamber of pleural collection system or (2) lead to a persistent negative pressure measured by the Chartis™ system

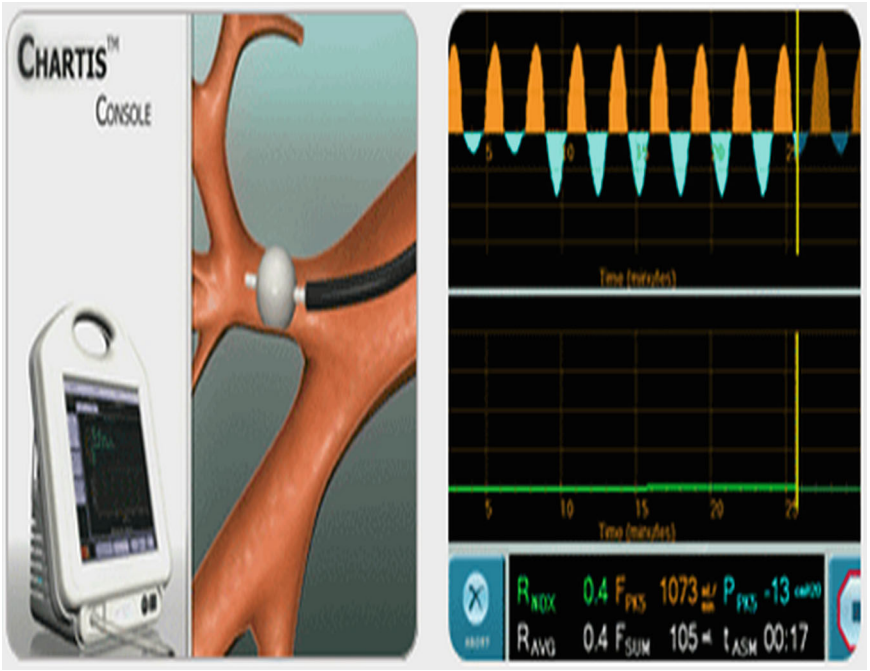

Fig. 5 Chartis™ system developed for endoscopic LVRS can be helpful in localizing a BPF. The balloon is inflated and a pressure sensor at the end of the balloon measures both pressure and flow distal to the occluded bronchus. A significant negative pressure during both inspiration and expiration indicates a segment involved in a BPF. (© 2010 Pulmonox. All Rights Reserved)

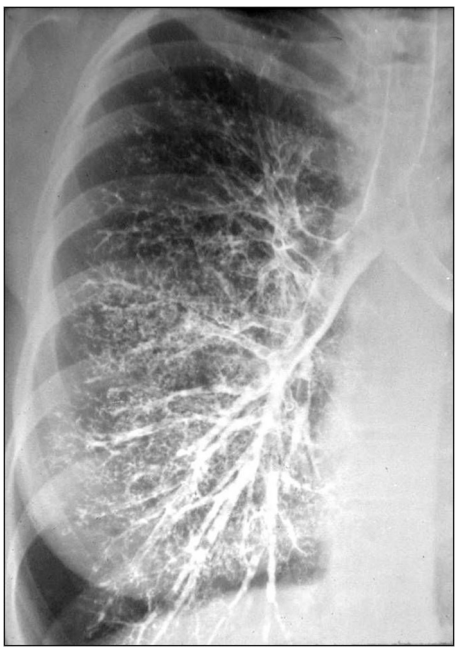

Fig. 6 Normal bronchogram. Contrast material is injected into the airway via a bronchoscope and fluoroscopy is performed. Extravasation of contrast material in the pleural space indicates the presence of a bronchopleural fistula. (Image courtesy of Stefan Tigges, M.D.)

nonionic low osmolar iodinated contrast medium (i.e., Omnipaque, GE Healthcare) is injected through a catheter placed through the working channel of a bronchoscope (Fig. 6). Fluoroscopy or CT can then be performed with visualization of contrast media extravasation from a site of a bronchopleural fistula. Scintigraphy with 99mTc-albumin (technetium-albumin) colloid fog inhalation has been described as a simple and accurate test for the detection of BPF. This is accomplished by aerosolization of a radiotracer and inhalation into the lungs with accumulation of the radiotracer at location of a BPF. This technique requires substantial time and cooperation on the part of a non-intubated patient and can be inconclusive in the setting of small fistulas or underlying lung disease such as COPD. Alternatively, ventilation scintigraphy with other radioactive tracers such as 81mKr (Krypton), 133Xe (Xenon), 99mTc-DTPA (technetium-labeled diethylenetriamine penta-acetate), and 99mTc-sulfur colloid has also been described. All of the advanced radiographic techniques mentioned above are now infrequently used with the advent and safety of balloon occlusion of the airway. Historically, bronchography was used for many years with excellent diagnostic accuracy.

5 Prognosis

In general, there is a high morbidity and mortality associated with bronchopleural fistulas. Historically, mortality ranged from 20% to 70%, depending on the underlying disease process. More recent data show lower mortality rates of 11–18% for BPF occurring within 30 days of surgery and of 0–7% for late BPF diagnosed after more than 30 days of surgery. Postoperative fistulas that can be surgically repaired have a lower morbidity and mortality than fistulas related to underlying malignancy or infection. Even with successful

intervention, mortality still can be as high as 40%. Death is usually related to a combination of aspiration and recurrent infections (pneumonia and empyema), which may lead to the development of acute respiratory distress syndrome and multiorgan system failure.

6 Treatment

6.1 General Principles

The initial management of any BPF should first address any immediate, life-threatening conditions, such as pleural space contamination, pulmonary flooding, or tension pneumothorax. A chest tube, if not already in place, should be inserted immediately to address these concerns. In complex cases with pleural adhesions and/or loculated hydropneumothoraces, multiple well-positioned, and/or image-guided chest tubes may be required. In the case of BPF due to a necrotizing lung or pleural space infection, a trial of antibiotics with adequate drainage should be attempted to decompress the pleural space, allowing time for full lung re-expansion and healing of the fistula. With severe necrotizing pneumonia, many weeks of antibiotic therapy, nutritional supplementation, patient rehabilitation, and chronic pleural space drainage may be required before contemplating surgery. In the majority of cases, an empyema associated with BPF is monomicrobial. *Staphylococcus* and *Streptococcus* are the most common pathogens. Although it is tempting to surgically close a fistula, active infection in the lung parenchyma or pleural space can lead to worse outcomes in the acute setting.

6.2 Conservative Therapy

Bronchopleural fistulas are very difficult to manage while the patient is on mechanical ventilation. Ventilator-delivered breaths will preferentially flow through the fistula as it represents the lowest point of resistance in the airway. This leads to difficulties with oxygenation and loss of exhaled tidal volumes and subsequent hypercapnia. Limiting airway pressure is an important strategy as continued airflow through the tract delays natural healing. Minimization of positive end expiratory pressure (PEEP), inspiratory flow rate, and tidal volume should be attempted to the extent tolerated by the patient. In large fistulas, selective intubation of the contralateral lung may be necessary to completely cease any airflow through the fistula. High-frequency oscillatory ventilation has been studied and found to be slightly more beneficial in patients with a proximal BPF and lack of parenchymal disease.

After initial drainage of the pneumothorax, the chest tube may actually contribute to the persistence of the BPF. In patients with minimal or no residual pneumothorax, suction should be removed and the chest tube placed on water seal. Keeping the chest tube on suction may have a paradoxical effect by "pulling" the defect open and contributing to the persistence of the BPF. Withdrawal of suction from the chest tubes minimizes airflow through the fistula to allow improved healing of the tract. Installation of a pleural sclerosing agent (talc, bleomycin, etc.) through the chest tube into the pleural space is often attempted as a minimally invasive method for sealing an air leak. The goal is to fuse (pleurodesis) the visceral and parietal pleura together, which will either contain the air leak or incite an inflammatory response to close the fistula. In order for this to be successful, the lung needs to completely fill the hemithorax so that there is good apposition between the visceral and parietal pleural surfaces. If a large pneumothorax is present, pleurodesis will not be achieved, and the air leak will persist. In general, a distinction should be made between early BPF after lung resection without empyema, in which rapid fistula closure should be attempted, and late BPF due to empyema and/or pleuropulmonary disease, in which a conservative approach over several weeks may be necessary.

6.3 Fistula Closure

Conservative measures (as described above) for closure of a bronchopleural fistula are necessary in patients who are poor surgical candidates or have small peripheral defects, which do not necessitate more aggressive intervention. In cases where conservative treatment fails, localization of the fistula is paramount in successful closure of the fistula either by semi-invasive (bronchoscopic) or invasive (surgical) management. There have been no large studies describing the optimal treatment or outcomes for bronchopleural fistulas nor does consensus opinion exist to suggest an optimal treatment in any particular situation. Regardless of the cause of the fistula, endoscopic and surgical treatment should not be viewed in isolation; instead, they can be complementary techniques.

6.4 Surgical Closure of BPF

If a postoperative BPF is detected within a few days of the patient's original surgery, re-exploration by either VATS or open thoracotomy with closure of the fistula is the recommended approach if the clinical situation allows. The success rate of BPF closure with surgery has been reported to be as high as 80–95%, although this includes the postoperative population that is healthy enough to undergo a major

reoperation. There are multiple surgical options described for closure of a BPF: (1) VATS/thoracotomy with direct resection and closure of the stump with intercostal muscle reinforcement or omental flap, (2) trans-sternal bronchial closure, (3) thoracoplasty with or without extrathoracic chest wall muscle transposition, or (4) chronic drainage with chest tube or Eloesser procedure (described below). Sequential operative procedures are often planned in debilitated patients who would not tolerate another major operation. Bronchopleural fistula complicated by empyema is one such circumstance where sequential operations may achieve better success. The pleural cavity is allowed to continuously drain by an empyema tube or an Eloesser procedure. The Eloesser procedure was named after Leo Eloesser, the thoracic surgeon who first described the technique. It involves the creation of a 5-cm opening in the chest wall with resection of two to three adjacent ribs and suturing of the skin to the pleural cavity to allow complete continuous drainage of the pleural space. The Eloesser procedure has minimal morbidity even in chronically ill patients and can be used in the acute setting. The patient then undergoes aggressive nutritional support and intensive physical rehabilitation and returns to the operating room once healthy enough to tolerate a second procedure for a thoracotomy with flap closure of the BPF. The details and technical aspects of surgical closure of bronchopleural fistulas are beyond the scope of this discussion. (Please see references at the end of this chapter for additional resources.)

6.5 Endoscopic Management of Bronchopleural Fistulas

6.5.1 Role of Brochoscopy

Bronchoscopy is indicated in all patients with a BPF. The bronchoscope has an important diagnostic role in visualization of the airway and/or surgical stump to examine for a central BPF or to identify the involved airway in a peripheral BPF (see Sect. "Diagnosis"). The flexible bronchoscope can also offer a wide range of therapeutic interventions (Table 3) as an alternative or adjunct to surgery to treat a bronchopleural fistula. Bronchoscopic fistula closure is typically indicated in patients who are at high risk for direct surgery, such as those with hemodynamic instability, severe hypoxemia, or advanced malignancy. However, endoscopic management and surgical repair should not be viewed as competing procedures; rather, they are complementary techniques. For example, treatment may involve two-staged intervention with endoscopic closure performed initially while the patient is acutely ill. Once the patient is more active and nutritionally replete, they can be offered the opportunity to undergo permanent surgical fixation of the fistula. In particular, patients with co-morbidities who cannot tolerate surgery may benefit from minimally invasive endoscopic BPF closure. This includes, for example, patients with malignant BPF who have received radiotherapy or chemotherapy. A retrospective case series has shown that distal, small BPF <6 mm can be closed endoscopically in 71.4–92.3% of cases, highlighting the potential of the bronchoscopic approach. Unfortunately, regardless of procedure, mortality still can be as high as 40% for patients with successfully treated bronchopleural fistulas. This high mortality underscores the critical nature and comorbidities of these patients and needs for further improvements in both endoscopic and surgical techniques.

Table 3 Endoscopic therapies available for treatment of BPF

Glues and adhesives
Fibrin glue (Coseal)
Polyethylene glycol (FocalSeal-L)
Albumin derivative (Cryolife)
Cyanoacrylate glue (Histoacryl)
Oxidized regenerated cellulose (Surgicel)
Sclerosing agents
Absolute ethanol
Antibiotics
Polidocanol–hydroxypoliethoxidodecane
Laser therapy/electrocautery
Cryotherapy
Stents
Silicone
Self-expanding metallic stents
Hybrid
Amplatzer occluders
Linear coils
One-way endobronchial valves
Zephyr valves
Spiration valves
Endobronchial Watanabe Spigot
Occluders produced by 3D Technology
Vascular occlusion coils

There are no large controlled trials to document the efficacy or superiority of any surgical or endobronchial closure procedure. No randomized trials have been performed, and recommendations are based on expert opinion and the treating physician's prior experience. The available small studies, case reports, and expert opinion agree that endoscopic closure is safe, well tolerated, and technically feasible in a majority of patients. Success rates vary considerably and are based on small series and isolated case reports. In one of the largest series (40 patients), improvement or resolution of the BPF occurred in 93% of patients treated endoscopically. Repeated procedures are often necessary; the average number of endoscopic intervention required per patient is 2.47 regardless of patient outcome.

6.5.2 Tissue Sealants and Glues

The first report of endoscopic closure of a BPF was by Hartmann in a one-page letter to the editor in Chest in

1977. He reported an IPF patient who underwent a resection of a right upper lobe (RUL) aspergilloma complicated by large BPF. The patient underwent successful closure with occlusion of the effected airway with tissue glue (methyl-2-cyanoacrylate). For centrally located fistulas, visualization by bronchoscopy can help in surgical planning. In nonsurgical candidates, such as described by Hartmann, closure can be attempted by application of sealant material to the airway defect via the bronchoscope. Small (<5 mm) fistulas are more likely to have successful treatment endoscopically, whereas large fistulas (>8 mm) are not suitable for endoscopic closure alone.

In order to close a fistula not seen in the central airways, complete occlusion of the airway (segmental or subsegmental) leading to the BPF will cease airflow through the fistula and allow eventual closure of the air leak. Application of a sealant or glue to "plug" the orifice of the affected airway will therefore cause atelectasis of the distal lung tissue while at the same time occluding airflow through the BPF. Initially, the bronchoscope is used to identify the involved segment by systematically inflating a balloon as described above. Once the airway is identified, sealant material such as fibrin glue or silver nitrate can be instilled through a catheter placed through the bronchoscope's working channel. Figures 7, 8, and 9 depict the process of applying a sealant to occlude a central BPF.

Multiple types of sealants and glues have been described, for example, albumin-glutaraldehyde tissue adhesive, oxidized regenerated cellulose, ethyl-2-cyanoacrylate, or silver nitrate; however, all initially work by plugging the defect. It typically will take a few minutes for the sealant to form a clot. Cough and forceful respiratory or mechanical ventilation therefore should be minimized for a few minutes after application. The sealant may swell to four times its volume over the next 24 h, completely filling in the fistula or occluding the airway. In the long run, the sealant causes an inflammatory reaction to induce tissue hyperplasia and scarring over the fistula. In animal models, glues induce foreign body granulomas and formation of granulation tissue. The glue is administered through a catheter inserted into the bronchoscope's working channel. Although the glue is injected directly onto a central fistula, it is sometimes necessary to provide a

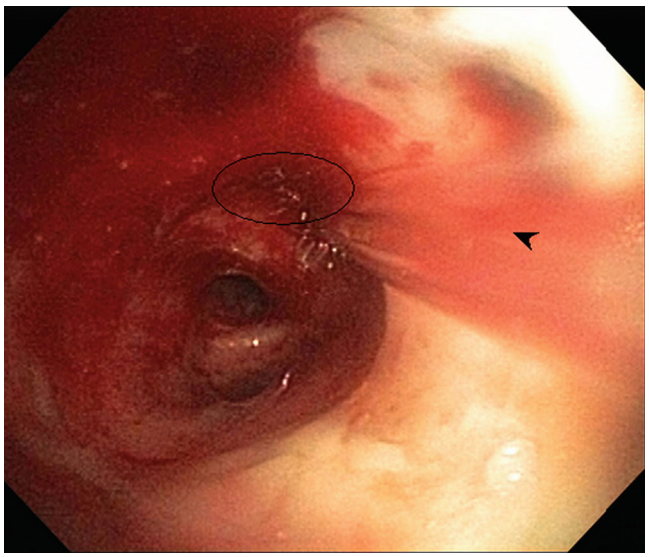

Fig. 8 Sealant administration catheter (*arrowhead*) located inside bronchopleural fistula (*circle*)

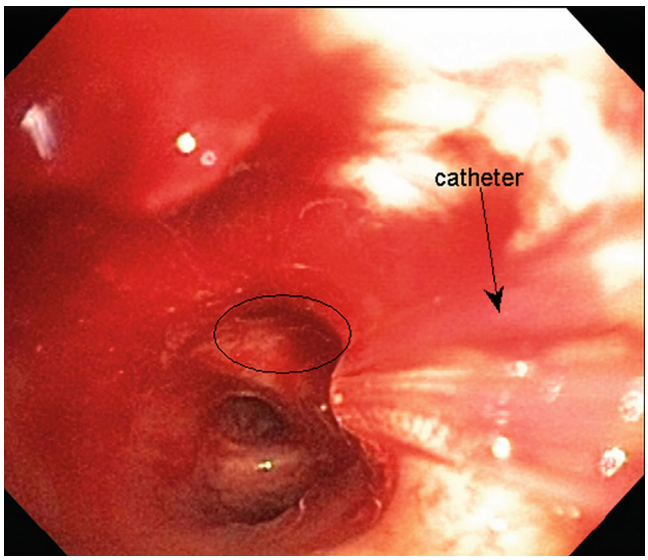

Fig. 7 Bronchoscopic view of distal left mainstem bronchus. There is a central bronchopleural fistula (*circled*). Also visible is catheter placed through working channel of bronchoscope approaching the fistula

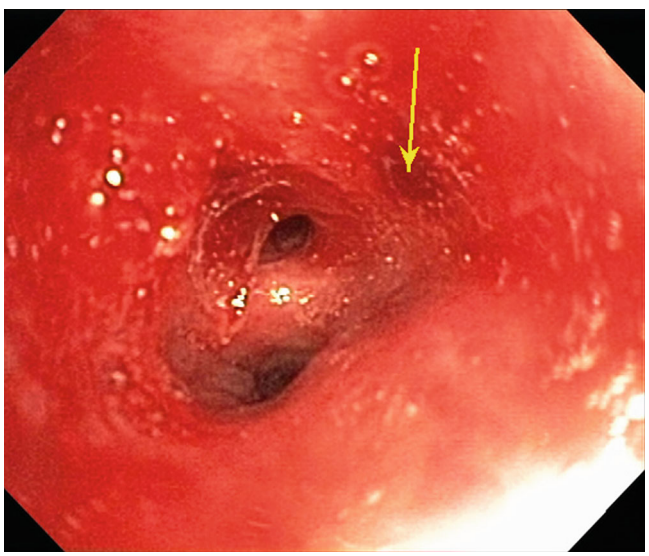

Fig. 9 Distal left mainstem bronchus after administration of sealant. Bronchopleural fistula now occluded with bioadhesive sealant (*arrow* denotes prior site of fistula)

Fig. 10 Coseal surgical sealant (Coseal, Baxter Healthcare, Deerfield, IL). Dry powder attached to syringe for reconstitution of compound prior to application. The two reagents activate when mixed to form the sealant clot

backbone for the glue to adhere. Spongy calf bone, which is both soft and elastic, can be cut and shaped into the form of the fistula. It can then be placed bronchoscopically into the fistula and then covered with fibrin glue. In a small case series ($n = 7$), covering the fistula with a polyglycolic acid mesh and fibrin glue showed a 100% success rate after an average of 2 bronchoscopies.

Currently, there are limited data comparing the safety, advantages, and disadvantages of the different occlusive agents. Further, sealants are generally more effective for closing peripheral air leaks than for sealing central fistulas involving the larger airways. Fistulas in central airways are typically larger and involve a prior surgical site. Larger airways also have more secretions, which makes it difficult for the sealant to dry and adhere to the airway and fistula. Airflow through the central airways is more robust than in the periphery, which makes it harder for the sealant to stay in appropriate position. Even if the sealant is initially successful, it may become dislodged in the future and require repeated administrations. Therefore, this technique is not suitable for a large proportion of BPFs.

Fibrin Glue

Fibrin glue is a two-component biologic adhesive, which forms a clot when the reagents (fibrin and thrombin) are mixed. It can be injected into the airway through a flexible polyurethane catheter (Duplocath, Baxter Healthcare, Deerfield, IL), which is inserted through the working channel of the bronchoscope. There are a number of commercially available forms of fibrin glue and biologic adhesives; one of the most common being Coseal (Baxter Healthcare, Deerfield, IL) shown in Fig. 10. A few mL of concentrated fibrinogen and thrombin is injected simultaneously into the airway through two separate channels in the catheter (Fig. 11). When the two compounds mix in the airway, a fibrin clot forms. Care must be taken to not to allow any excess glue in liquid form to come into contact with the bronchoscope. Within a few minutes, the sealant will congeal in the airway and occlude the fistula. Any excess glue, once congealed, should then be removed bronchoscopically to prevent occlusion of the normal airway lumen (Fig. 12).

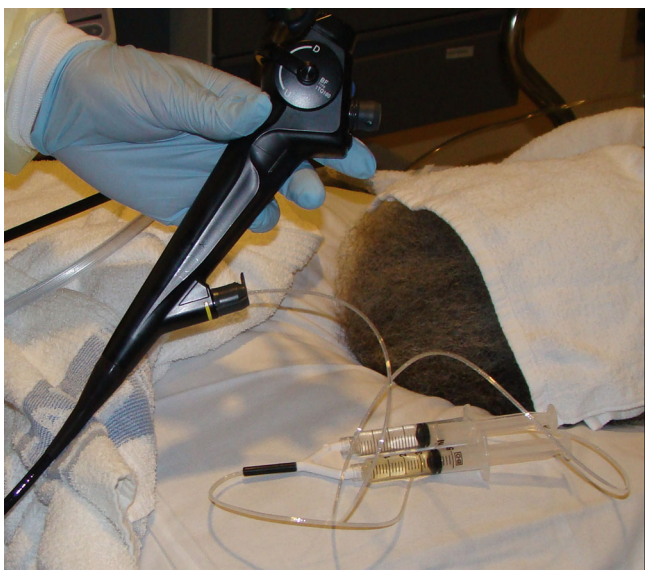

Fig. 11 Reconstituted Coseal attached to administration catheter. The catheter is then placed through working channel of bronchoscope

Over the next 24 h, the clot will expand and seal off the airway. The clot that forms is gradually reabsorbed, and thus, long-term scarring or damage to the airways is uncommon. Since fibrin is degraded, if the fistula has not healed by the time the fibrin is reabsorbed, then the fistula may recur.

Single-channel catheters are also available for administration of the reagents. Since the compounds harden when they are exposed to each other, it is felt safer to inject them through a dual-chambered catheter running through the working channel rather than sequentially through a single-chamber catheter. If any residual reagent is left in the working channel, when it comes into contact with the other compound, it will clog the working channel. It is recommended not to pull the catheter back through the working channel of the bronchoscope for two reasons: (1) wet fibrin at the end of the catheter can stick to the inside of the bronchoscope, ruining the working channel, or (2) dried fibrin glue adherent to the tip of the catheter can scratch the inside of the bronchoscope also requiring replacement of the working channel. Instead, the catheter and bronchoscope should be removed from the patient as a single unit and the tip of the catheter cut and inspected before pulling the remaining catheter back out through the bronchoscope.

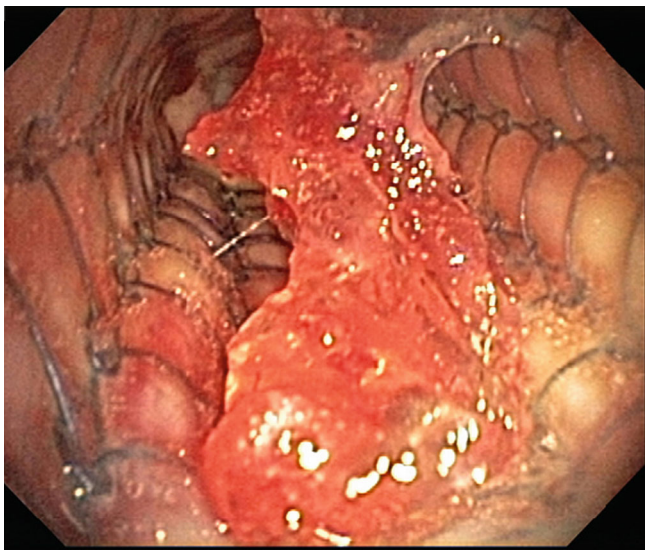

Fig. 12 Excessive fibrin glue in airway after administration. Once glue congeals, it can be easily removed with bronchoscope

Care must be taken to ensure the injection catheter is far enough away from the bronchoscope so that the sealant will not accidentally come into contact with the scope (Fig. 13). Glues that adhere to the scope will cause permanent damage to the lens or exterior of the scope. At no time should suctioning occur while sealant is in the airway. Suctioning of any amount of glue or sealant into the working channel of the bronchoscope will allow the glue to harden within the channel, thus permanently obstructing the working channel. Care must be taken during the initial insertion of the catheter through the working channel of the bronchoscope. Many catheters are thin walled, and a slight kink or bend in the catheter will cause the catheter to tear and sealant to leak into the working channel of the bronchoscope leading to irrecoverable damage. Forcefully injecting the sealant likewise will cause trauma to the catheter leading to leakage. If the sealant hardens within the catheter, the entire catheter must be removed and discarded. It is never a good idea to try to forcefully expel hardened sealant.

Fig. 13 Catheter extending through bronchoscope. Tip of catheter placed at distance far enough that administered sealant will not accidentally come into contact with bronchoscope

Other Adhesives and Sealants

Overall, a wide variety of sealing materials were reported, some examples of which are given below. However, there are no prospective studies comparing the advantages and disadvantages of these different agents. Cyanoacrylate glue polymerizes and becomes solid when coming into contact with body fluid or tissue. An early report described two patients with postoperative BPF successfully treated by application of the cyanoacrylate glue through an epidural catheter placed in the working channel of a flexible bronchoscope. One milliliter of glue was instilled directly on the defect.

BioGlue (Fig. 14) has been applied surgically to BPFs in patients during VATS or thoracotomy. The adhesive is made from an albumin derivative. It has been helpful for covering lung lacerations or dehiscence at suture or staple lines. Only one patient has been reported to have undergone endoscopic administration of BioGlue by rigid bronchoscopy.

Polyethylene glycol (FocalSeal-L, Focal; Lexington, MA) was FDA-approved as a water-soluble polyethylene glycol-based gel. It is "painted" into the airway through the working channel of the bronchoscope. Once activated by light, the sealant forms. This is usually accomplished on external surfaces by the use of a xenon-generated wand, which emits light in the spectrum of 440–550 nm. In one selected case report, the sealant was activated by the use of an autofluorescence bronchoscope which emits a blue light from the scope at 442 nm. This case described the successful closure of a 4-mm dehiscence at a bronchial stump using this method.

Oxidized regenerated cellulose (Surgicel, Ethicon Piscataway, NJ) is a mesh-like sheet of inert material, which is typically used to cover a laceration or to control bleeding. It induces fibrinogenesis and mechanically occludes a defect. There is an isolated report of Surgicel used to close a central left mainstem BPF in a patient with advanced lung cancer. A flexible bronchoscope was used to guide the placement of several pieces of Surgicel to mechanically cover the defect. Surgicel does not have any adhesive properties; therefore, to prevent dislodgement of the Surgicel, a Fogarty catheter balloon was inserted nasally and used to pack the Surgicel into the BPF. The Fogarty catheter was then removed 48 h later with complete closure of the fistula, and the patient was discharged to home a few days later.

6.5.3 One-Way Endobronchial Valves

Endobronchial valves were originally developed for endoscopic lung volume reduction (ELVR) and therefore have the advantage of being widely established. As a one-way valve, they allow for unidirectional air and secretion flow out of the lung parenchyma but not back in. By preventing airflow back through the affected airway, the air leak is minimized, and the fistula may eventually close. Two valves are commercially available and shown in Figs. 15 and 16. The Spiration system (Spiration, Inc. Redmond, WA) contains a one-way valve composed of a nitinol frame and polyurethane umbrella-shaped membrane. It has been approved for compassionate human use in the United States by the FDA since 2008 (HO60002) for prolonged air leaks. The Zephyr endobronchial valve (Pulmonx, Redwood City, CA) is a self-expanding silicone valve with a nitinol backbone. Both valves can be placed through a delivery device, which fits through a 2.8-mm bronchoscopic working channel and are

Fig. 14 BioGlue sealant in packaging (Cryolife; Kennesaw, GA). Prefilled syringe for administration of tissue sealant

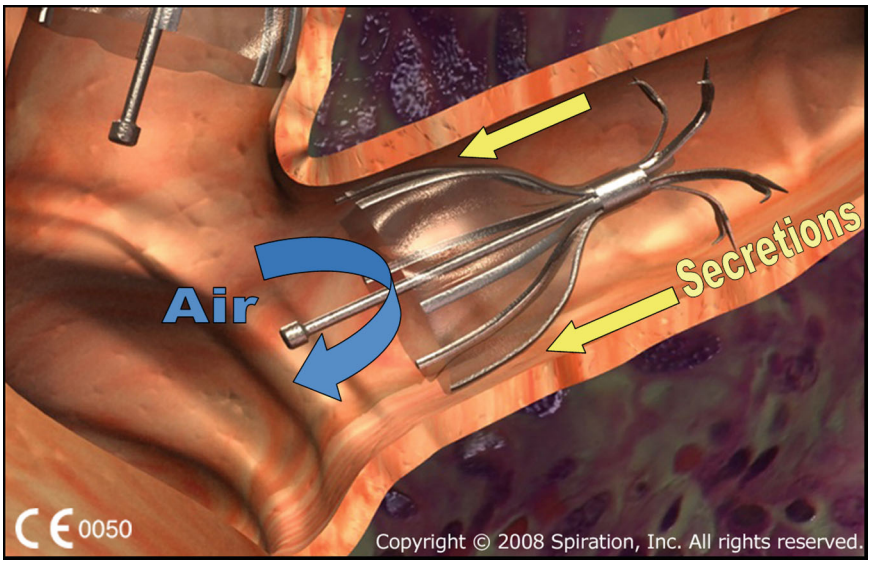

Fig. 15 The Spiration valve is a one-way umbrella-shaped endobronchial valve that is deployed via a flexible bronchoscope. It allows for unidirectional air and secretion flow out of the lung parenchyma but not back in. (Printed with permission from Spiration, Inc.)

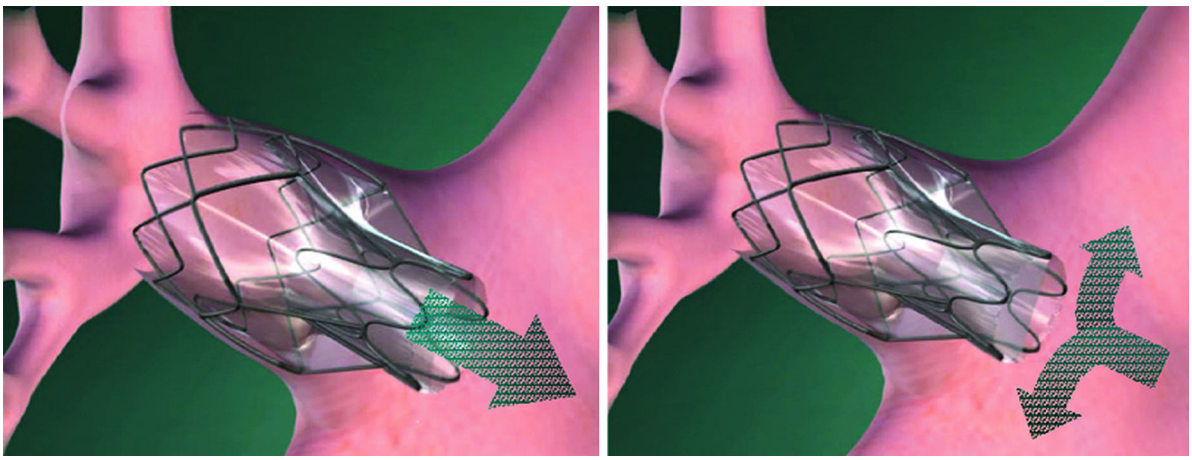

Fig. 16 The Zephyr EBV deployed in an airway. It is a self-expanding silicone valve placed via flexible bronchoscope to allow unidirectional air and secretion flow out of lung parenchyma to assist in closure of a BPF. Air flows from parenchyma to central airways during exhalation (**a**, *left*) but cannot flow back through the valve during inspiration (**b**, *right*). (© 2010 Pulmonox. All Rights Reserved)

designed to be able to be removed once the air leak has resolved. It is recommended to start considering valve removal after 6 weeks after placement o upon resolution of the air leak to minimize long-term airway complications such as infection, valve migration, or tissue hyperplasia and stenosis around the foreign body (valve).

There is a growing body of literature and research on the use of valves for fistula closure. However, the evidence remains limited due to the difficulty of conducting controlled trials and randomization. A recent analysis of a nationwide US database on the treatment of persistent air leak with Spiration valves found an increasing use of Spiration valves from 2007 to 2016, with an in-hospital mortality rate of 8.8% and a stable associated composite mortality rate of 33.8% since 2012. Further, a current literature review from 2024 by Smessein et al. summarized 19 studies, six of whom prospective, with persistent air leak resolution ranging from 42% to 100% in 1–30 days. The authors also performed a European multicenter case series on endobronchial valve treatment for persistent air leaks in 66 high-risk patients, mostly with COPD or lung cancer. Success rate was 60%, and the complication rate was low. In the same year, Huh et al. showed Asian data of 18 patients with persistent air leak, who could be successfully treated in 78% of cases. These are promising results, especially considering patients intolerant to surgical treatment. As with ELVR, fissure integrity to the adjacent lobes appears to be important in BPF closure with valves: In a retrospective analysis, Majid et al. showed that PAL resolution was successful in 14/16 patients (88%) without collateral ventilation and in only 4/10 patients (40%) with collateral

ventilation on Chest CTs. These results suggest that endobronchial valve placement appears to be a safe and effective intervention for prolonged air leak from various cases.

6.5.4 Stents

The first reports of using stents to cover fistulas were described in patients with esophageal to airway fistulas. A majority of these stents were silicone and used to cover the airway defect and prevent further aspiration of gastroesophageal contents and contamination of the airway and lung parenchyma. Patients who already have an esophageal stent placed are at high risk of the stent eroding through the thin posterior membrane of the trachea and bronchus. Cases have been reported of an esophageal stent eroding into the trachea leading to complete airway occlusion and subsequent asphyxiation. As such, airway stents are sometimes placed after an esophageal stent prophylactically to maintain airway patency rather than to cover the defect. Double stenting (esophageal and airway), intended only for palliative purposes, has been reported to improve patient symptoms and possibly improve survival.

A large variety of airway stents are available to cover a bronchopleural fistula. Acutely, stents are placed to provide a mechanical occlusion of the airway defect to prevent further contamination of the airway or pleural space and leakage of air (Fig. 17). Over time, however, the stent causes a foreign body reaction leading to granulation tissue formation, which hopefully will fill in the fistula with inflammatory tissue. Stents used to cover an airway defect typically have some occlusive material (e.g., silicone or polyurethane) in order to block the flow of air or secretions through the fistula. Commonly placed stents for this purpose include silicone stents (Tracheobronxane Dumon, Novatech, Westborough, MA), hybrid stents (Aero, Alveolus Inc., North Carolina), and self-expanding metal stents (Ultraflex, Boston Scientific, Natick, MA and Silmet, Novatech, Westborough, MA). The more recently developed anatomically shaped J-Carina stent (aerstent TBJ, Leufen Medical GmbH, Berlin, Germany), a covered nitinol stent with atraumatic ends, can also be used to bridge a BPF. The stent is delivered via a reloadable delivery system and can be repositioned as required. Metal stents should be used cautiously in patients with nonmalignant or surgically resected malignant disease. Metallic stents come either uncovered or covered with a thin piece of silicone or polyurethane. As an uncovered stent has openings between the metallic backbone, it will not physically occlude the fistula. The metallic stent will cause an inflammatory response in the airway, which will allow the fistula to close over time. Given that these stents will quickly embed into the airway, it is recommended that they be removed as soon as possible in patients with nonmalignant airway disease.

A few specifically tailored bronchial occluding stents have been described. These typically are self-expandable metal stents completely covered in silicone or polyurethane. They are designed for large fistulas from surgical site dehiscence and deployed across a fistula. The proximal end of the stent appears normal and remains in the intact airway. The distal end of the stent is a blind pouch so that there is no direct communication between the airway and the pleural space. These stents have to be custom made and are not widely used at the current time.

Regardless of the type implanted, stents are foreign bodies and can be associated with significant complications such as mucus plugging, granulation tissue formation, stent

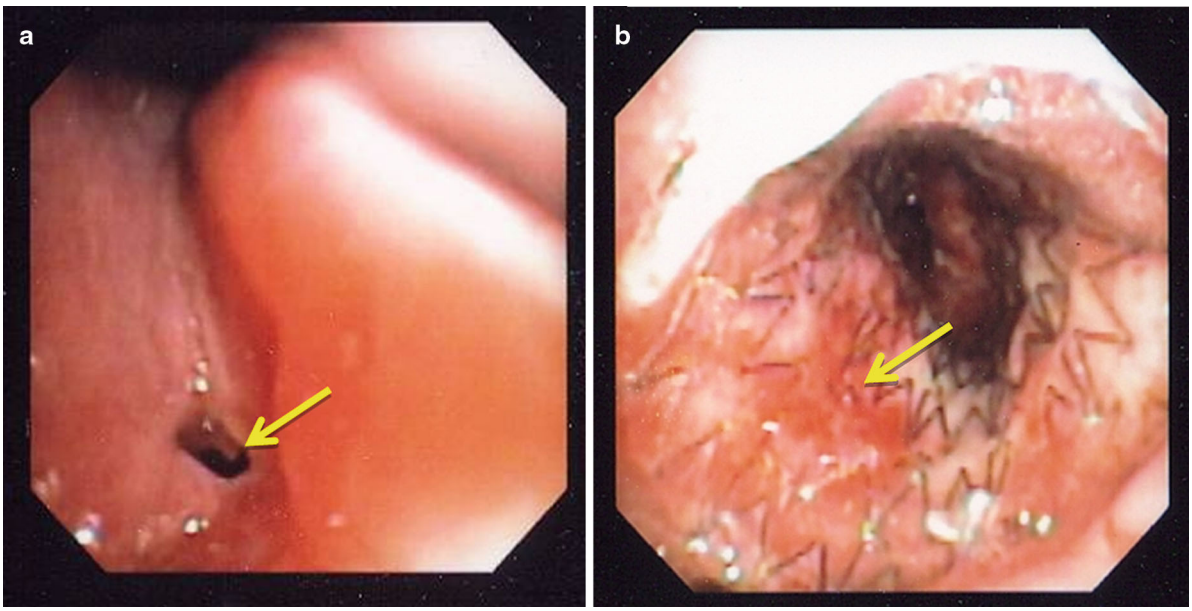

Fig. 17 Bronchopleural fistula (*arrow*) in right mainstem covered by a hybrid stent

migration, and infection. Post-interventional stent management with regular endoscopic maintenance and intensive inhalation therapy is therefore of great importance.

6.5.5 Cardiac Occluders

Another option for BPF closure is Amplatzer occluders, which were originally developed to treat cardiac atrial-septal or ventricular-septal defects. They consist of two self-expanding Nitinol discs with polyester patches that are centrally connected. Available sizes range from 4 to 40 mm in diameter allowing for the treatment of even larger fistulas >8 mm. The Amplatzer device can be deployed via a catheter under visual control and closes the defect with its self-centering waist. If the position needs to be corrected, the Amplatzer device can be easily reinserted into the catheter. Furchter et al. were able to show in a retrospective analysis that BPFs could be adequately closed with an Amplatzer occluders in 30 of 31 patients. There were no treatment-related complications and no recurrences during the long-term follow-up of 17 months. These data support that endobronchial closure of BPF using Amplatzer devices may be a promising method to close BPF. However, the Ampaltzer approach is still an "off-label" treatment used according to the expertise of the treating center and the wishes of the patient.

6.5.6 Endobronchial Spigots

Endobronchial Watanabe Spigots (EWS) are silicone bronchial plugs that can be inserted into the target bronchi responsive for the fistula to prevent air entry. They are marked with barium sulfate for radiological visibility, tapered according to airway anatomy and available in three diameters (5, 6, and 7 mm). To prevent migration, the spigots are fitted with studs on the outside. However, dislocation is a frequent adverse event, and antitussives are recommended after implantation. The spigots must be removed when the BPF is closed. In a small retrospective study on 21 patients, Himeji et al. described a chest tube removal rate was 85.7% after EWS implantation. A recent analysis of a Japanese national database of 1095 patients who underwent bronchial occlusion with the endobronchial spigots between 2014 and 2022 showed a treatment failure rate of 36.8% and an in-hospital mortality of 23.0%. The main risk factors for therapy failure were age >85 years, male sex, low Bathel score, interstitial pneumonia, antibiotic and steroid treatment, and previous surgery for bronchial occlusion. The best method for placing the EWS is currently being researched.

6.5.7 Additional Endoscopic Therapies

Vascular occlusion coils (Gianturco or Platinum Coil Vascular Occlusion System, Boston Scientific Co., Fremont) in combination with *n*-butyl-2-cyanoacrylate (Histoacryl; B. Braun Melsungen AG, Germany) have been placed endobronchially to occlude the airway leading to peripheral BPFs. The use of the coil in combination with cyanoacrylate may provide a scaffolding for the sealant and account for the successful closures. At least seven cases have been reported with mixed success using vascular coils.

Sclerosing agents can also be used to induce fibrosis and scarring over of the fistula. Electrocautery or laser therapy can be directly applied to a central lesion or used to "scar" or stenose the airway leading to a BPF. Either therapy, however, can also cause tissue necrosis and expand the size of the fistula. Further, cryotherapy has been proposed to induce scar formation. Sclerosis can be accomplished with topical agents. Takaoka et al. described the closure of five patients with a postoperative BPF using absolute ethanol. All fistulas were located in central airway, were less than 3 mm, and were visible by bronchoscopy. Absolute ethanol in 0.1-mL aliquots was injected into the mucosa around the fistula using an injection needle (NM-21 L; Olympus) through the working channel of the bronchoscope. Up to 41 injections were performed during a single bronchoscopy, and one patient required four bronchoscopies to complete the closure. All patients had successful closure with range of time from onset to closure of 6 days to 15 months. The ethanol causes rapid dehydration of tissue and induces scar formation. No complications were noted; however, caution must be exercised to prevent excess injection of the absolute ethanol. Excessive injection may cause local tissue necrosis. Spillage of excess ethanol into the airway causes scarring of normal endobronchial mucosa. Recently, it was proposed to conduct submucosal ethanol injections with endobronchial ultrasound guidance.

Sclerosis may also be accomplished with topical administration of other agents. One report of intrabronchial administration of doxycycline has been described in a 17-year-old man with a BPF that developed as a result of ARDS. Once the involved subsegmental airway was identified, 0.5 g of tetracycline suspended in 25 mL of sterile water was administered through a No. 5 Fogarty catheter. A blood patch was then created using 10 cc of autologous non-heparinized blood injected through the catheter. The air leak resolved, and the patient was subsequently able to wean from mechanical ventilation, and a follow-up bronchoscopy 2 weeks later demonstrated almost complete stenosis of the orifice of the treated subsegment. Polidocanol–hydroxypoliethoxidodecane (Aethoxysklerol Kreussler) is mainly used for the sclerosing of veins (varicose or esophageal) but has been used in at least 35 patients with bronchopleural fistulas. When injected (4–5 mL of 2% polidocanol) submucosally around the edges of a fistula, it causes an initial whitish reactive edema followed by hyperemic and thickened tissue (granulation tissue). The procedure is repeated until the fistula fills in and a fibrous scar is permanently formed.

As described earlier, balloon catheter-directed occlusion of subsegmental airways is used diagnostically to identify a peripheral air leak. The balloon, however, could be used therapeutically to block airflow through the fistula. There is at least one report of a nonsurgical patient who had a balloon left in place for weeks to therapeutically occlude a BPF. The patient in this report did not have a favorable outcome.

Currently, local bronchoscopic implantation of pluripotent mesenchymal stem cells (MSCs) is an emerging idea to close the BPF through fibroblast proliferation and collagen formation. MSC was first used for BPF treatment in 2015 by Petrella et al. However, this approach is still at an experimental stage and requires further investigation. Further, it is discussed that the emerging technology of three-dimensional (3D) printing will play an increasing role in the design of customized stents and devices.

7 Conclusion

Bronchopleural fistulas are infrequently seen but have a high mortality even after successful treatment. They occur most commonly after pulmonary resection and may be seen in infections, malignancy, or as a complication of cancer treatment. Bronchoscopy is indicated in all patients with BPF and can be helpful in both diagnosis and treatment of the BPF. When conservative measures fail, it is best to evaluate the patient for both endoscopic as well as surgical closure. There is a lack of evidence over optimal treatment method as no large or randomized trials have been performed. Multiple endoscopic therapies have been described on the basis of a few small series and case reports. No one therapy will be preferred in all patients. The clinical scenario as well as patient and physician preference will be the main factors influencing treatment.

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