CHEST

Management of Persistent Air Leaks

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Alveolar-pleural fistulas causing persistent air leaks (PALs) are associated with prolonged hospital stays and high morbidity. Prior guidelines recommend surgical repair as the gold standard for treatment, albeit it is a solution with limited success. In patients who have recently undergone thoracic surgery or in whom surgery would be contraindicated based on the severity of illness, there has been a lack of treatment options. This review describes a brief history of treatment guidelines for PALs. In the past 20 years, newer and less invasive treatment options have been developed. Aside from supportive care, the literature includes anecdotal successful reports using fibrin sealants, ethanol injection, metal coils, and Watanabe spigots. More recently, larger studies have demonstrated success with chemical pleurodesis, autologous blood patch pleurodesis, and endobronchial valves. This manuscript describes these treatment options in detail, including postprocedural adverse events. Further research, including randomized controlled trials with comparison of these options, are needed, as is long-term follow-up for these interventions. CHEST 2017; 152(2):417-423

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An alveolar-pleural fistula is a communication between the alveoli and the pleural space. This connection will lead to the development of a pneumothorax as air escapes the lung into the pleural cavity. If this connection persists, there will be flow of air from the lung parenchyma to the pleural space and worsening of the pneumothorax. Once a chest tube is inserted, air bubbling into the chest drainage system indicates an air leak. The flow of air through the fistulous tract into the pleural space delays healing and inhibits lung expansion. Although a majority of pneumothoraces resolve with thoracostomy tube drainage, many continue days after the lung injury. If an air leak lasts > 5 to 7 days, it is termed a persistent air leak (PAL). A PAL is commonly caused by a spontaneous pneumothorax from underlying lung disease (secondary spontaneous pneumothorax), pulmonary infections, complications of mechanical ventilation, following chest trauma or after pulmonary surgery.

There have been a few proposed classifications that attempt to quantify the severity of PALs in the postoperative setting, including the most cited classification by Cerfolio[1] which grades the PAL based on whether the leak is expiratory or continuous and the amount of air leak (Table 1).

Further categorization can be done by observing the water seal chamber on the drainage system. Most chest drainage systems have three chambers. The first chamber collects fluid or blood from the

ABBREVIATIONS: EBV = endobronchial valve; IBV = intrabronchial valve; LVRS = lung volume reduction surgery; PAL = persistent air leak

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TABLE 1] Cerfolio Classification of Air Leaks

Grade 1, FE	During forced expiration only, typically when asking the patient to cough
Grade 2, E	Expiratory only
Grade 3, I	Inspiratory only
Grade 4, C	Continuous bubbling present in the air leak chamber during both inspiration and expiration. These leaks tend to be large and are more likely to be seen in patients receiving positive-pressure ventilation.

patient. The second chamber is the water seal chamber. It allows air to exit from the pleural space on exhalation and prevents air from entering on inhalation. Air bubbling in the water seal chamber indicates an air leak. The third chamber regulates the amount of suction applied through the system.[2] Typically, there is an air leak meter that indicates the degree of air leak, measured in columns from 1 to 7. The higher the numbered column through which bubbling occurs, the larger the air leak. In an attempt to bypass a relatively subjective scale of assessing the size of a leak, new digital chest drainage systems allow direct quantitation of flow through the drainage system.[3] These digital drainage devices display the flow (in mL/min) along with the pleural pressure difference (maximum – minimum pleural pressure) in real time. In general, once the air leak is < 20 mL/min, a chest tube can be safely removed. A few small randomized controlled trials have shown reductions in the duration of chest tube placement and hospital length of stay when a digital drainage device was used when compared with conventional drainage devices.[4]

Incidence of Persistent Air Leaks

A pneumothorax during mechanical ventilation is considered a serious complication of ventilator therapy. It can lead to poor lung expansion, ventilation/perfusion mismatch, direct extension of airway infection to the pleural space, and an inability to maintain positive end-expiratory pressure. In a retrospective study of mechanically ventilated patients (surgical, medical, coronary, and burn ICUs), over a 4-year period, 39 of 1,700 patients had PALs defined as lasting for > 24 hours. Overall mortality was 67%, but when looking at nontrauma patients, the mortality was 92%.[5] Of note, this study was performed prior to standardization of low tidal volume ventilation for lung protection, and average tidal volumes during this study were 14.6 mL/kg. Therefore, the incidence of alveolar-pleural fistulas in mechanically ventilated patients is likely much lower in the era of lung-protective strategy for mechanical ventilation.

PALs are common after thoracic surgery, especially in patients undergoing lung volume reduction surgery (LVRS) and resection. In patients undergoing lobectomies, the incidence of PAL was up to 26%.[6-9] For lobectomies, the main issue with PALs is inadequate parenchyma to fill the hemithorax after lung resection rather than collapsed lung per se. In this scenario, it is implied that apposition will not occur immediately after resection and that an air leak can be expected to persist while allowing conservative therapy more time to work. Using digital flow and pressure monitors in patients undergoing lobectomies, a leak > 50 mL/min or a larger pleural pressure difference (measured over 6 hours) postoperatively was predictive of a PAL lasting longer than 72 hours.[10] In patients undergoing LVRS, DeCamp et al[11] found an incidence of PAL of 46% at 7 days post LVRS. The incidence of PALs is higher following LVRS (24%-46% incidence) when compared with lobectomies (8.3%) and wedge resections (3.3%).[11,12]

Regarding nonsurgical procedures, such as needle aspiration and transbronchial biopsies, our literature search did not identify any original articles citing the incidence of PALs. However, the incidence of pneumothorax following transbronchial biopsy is 0% to 6%. A recent retrospective review by Garcha et al[13] of 1,498 patients undergoing transbronchial biopsies cited an incidence of pneumothorax of 0.009%. Therefore, the incidence of PAL following transbronchial biopsy is likely very small.[13,14]

Risk Factors for the Development of PAL

In patients undergoing lobectomy, risk factors for PAL include the following:

- COPD[7]
- Female sex
- Lower FEV_1
- History of smoking[6]
- Diabetes mellitus
- Chronic steroid use[15]

In the cohort of patients post LVRS, a PAL was more likely to occur in patients with the following:

- Lower diffusing capacity of lung for carbon monoxide and lower FEV_1
- Marked pleural adhesions noted during surgery
- Upper lobe/diffuse emphysema rather than lower-lobe-predominant emphysema[11]

In a recent prospective study of patients following video-assisted thoracoscopic surgery for spontaneous pneumothorax, PAL was more common in patients with underlying lung disease (31.3% vs 3.8%), increased age, and larger bullae diameter.[16]

Complications of PAL

In patients undergoing either LVRS or lobectomy, mortality was similar among those who did and those who did not experience an air leak. Although a PAL may not have an impact on mortality, it has a clear and strong effect on morbidity. Patients with a PAL had increased complications, including ICU readmission, pneumonia, and a longer hospital stay (Table 2).[6,11]

Guidelines for Treatment of PAL

Based on the most recent American College of Chest Physicians guidelines published in 2001 on spontaneous pneumothoraces resulting in a PAL, the panel recommended observation with a chest tube for 4 days for spontaneous closure of the fistula. Patients with a PAL that persisted beyond 4 days should be evaluated for surgery to close the air leak followed by pleurodesis to prevent recurrence. Given the parenchymal toxicity of sclerosing agents, chemical pleurodesis by instilling talc slurry or doxycycline was considered contraindicated except in circumstances in which surgery was contraindicated or in patients who refused an operative procedure.[17] At that time, bronchoscopy to seal endobronchial sites of air leaks was not recommended. These recommendations are similar to the 2010 British Thoracic Society guidelines on pleural disease in which the panel recommended that "in cases of persistent air leak or failure of the lung to re-expand, an early (3-5 days) thoracic surgical opinion should be sought" without any further recommendations if the patient was a poor operative candidate.[18]

TABLE 2] Length of Stay in Patients With PAL (by Surgery Type)

Lobectomy LOS (n = 134)		LVRS LOS (n = 552)	
Non-PAL	PAL > 7 d	Non-PAL	PAL > 7 d
7.9 ± 1.44	13.7 ± 3.92	7.6 ± 4.4	11.8 ± 6.5
($P = < .01$)		($P = .0005$)	

LOS = length of stay; LVRS = lung volume reduction surgery; PAL = persistent air leak.

Treatment Options

For PALs in patients who have recently undergone thoracic surgery or in whom surgery would be contraindicated based on the severity of illness, there has been a lack of treatment options or expert consensus regarding best practice. Prior to the past 2 decades, conservative management with prolonged chest tube drainage was the treatment of choice. Attempts with sealants, Watanabe spigots, metal coils, alcohol sclerosis of the airways, and many other interventions have been reported; all were anecdotal with variable success (Table 3).[19-28] Chemical pleurodesis, autologous blood patch pleurodesis, and most recently, endoscopically placed "one-way" valves to temporarily "plug" the airway have been successful.[29,30] The current strategies on the management of PAL are detailed in the following sections.

Conservative Management

There are three major factors to consider when initially evaluating an air leak: volume, duration, and trend of the leak. For example, a larger air leak that has been present longer without any improvement has a low likelihood of resolution, whereas a smaller air leak that is improving daily is more likely to resolve spontaneously.[31] In the absence of a bronchopleural fistula, the majority of postoperative air leaks will resolve over time, even if that time involves weeks.

When patients with air leaks are receiving positive-pressure ventilation, daily spontaneous breathing trials with the goal of early liberation from mechanical ventilation are ideal, as positive pressure may worsen the size of the air leak and impair the ability to heal. While the patient is receiving positive-pressure ventilation, reducing the inspiratory time, end-expiratory pressure, and tidal volume can help diminish the air leak.[32]

In an initial study on air leaks, a management algorithm was prospectively applied to the chest tubes of all patients who underwent pulmonary resection. This study demonstrated the safety of placing a chest tube to water seal when a patient experienced a PAL postoperatively.[33] Following this study, a randomized controlled trial compared placing the chest tube to suction 1 day after pulmonary resection vs placing the chest tube to water seal.[34] This trial showed a statistically significant advantage by postoperative day 3 in those air leaks placed to water seal rather than suction. In the patients who had been randomized to placing the chest tube to suction, once the chest tube was placed to water seal (crossover portion of the study), the air leak resolved within 1 day in 13 of the 14 patients. Numerous

TABLE 3] Anecdotal Approaches

Method	Type of Study (No. of Patients)	Air Leak Improved or Resolved	Complications
Fibrin sealant administered through bronchoscopy[20]	3 case reports (1 patient each)	3 of 3	None reported
Fibrin sealant administered through thoracoscopy[21]	Case series (12)	11 of 12	None reported
Platelet gel[22]	Case report (1)	1 of 1	None reported
Ethanolamine[23,24]	2 case series (15 and 5)	12 of 15, 5 of 5	First case series: fever (53%), chest pain (27%), pulmonary infiltrates (83%), and hydropneumothorax (7%) Second case series: none reported
Metal coils[25]	Case series (5)	4 of 5	None reported
Watanabe spigots[26]	Case series (60)	58 of 60	Pneumonia (3%), dyspnea (3%), fever (1%)
Laser[27]	Case series (13), abstract	11 of 13	None reported
Synthetic hydrogel[28]	Case series (22)	19 of 22	Hydrogel expectoration (9%), hypoxia (5%)

studies, including those by Brunelli et al[35] and Alphonso et al[36] have attempted to answer this question with differing results. There still is not a consensus as to "on or off" suction for management.

If placing the chest tube to water seal fails to resolve the air leak, discharge with an ambulatory one-way valve (Heimlich valve) is another option to reduce hospital length of stay. Henry Heimlich developed a one-way tube in the 1960s in which air and fluid are only able to flow one way, from the pleural space to outside the chest wall. These one-way valves are small and allow the patient more freedom to ambulate.[37] In a study of 107 patients post-LVRS for emphysema, 25 patients experienced a prolonged air leak that lasted > 5 days. Each patient with a PAL received a Heimlich valve to facilitate earlier hospital discharge, no matter the size of the air leak. Each patient was seen daily for pulmonary rehabilitation and dressing changes. If one assumes that these patients would have remained hospitalized until chest tube removal, the Heimlich valve shortened hospital stay by 46%. Only one of the 25 patients required readmission for subcutaneous emphysema that resolved with placing the chest tube drainage to suction. This small case-control trial demonstrated the safety of one-way valves and outpatient follow-up for PALs.

Another study by Cerfolio et al[15] showed the safety of chest tube removal if a PAL remained after the patient was discharged home with a Heimlich valve, as long as the patient was asymptomatic without subcutaneous emphysema and the pneumothorax had not increased in size.

Conservative management, including ventilator strategies to reduce fistula flow, placing the chest tube to water seal, discharge home with a one-way valve, or a combination, have all been shown to be beneficial in the treatment of PALs. However, in some cases, these strategies are not successful or practical and further interventions are needed.

Chemical Pleurodesis

Sclerosants are chemicals that cause an inflammatory response and, when administered into the pleural space, allow for sealing of the pleural space, cessation of an air leak, and prevention of recurrent pneumothorax. Common sclerosing agents include talc, doxycycline, tetracycline, minocycline, bleomycin, and OK-432 (mixture of a low-virulence strain of *Streptococcus pyogenes* incubated with benzylpenicillin). In a retrospective analysis by Liberman et al,[6] 40 of 41 patients with a PAL postlobectomy were successfully treated with talc pleurodesis. In another retrospective study of patients with PALs following thoracoscopic operations for primary spontaneous pneumothoraces, 38 of 60 were successfully treated with minocycline pleurodesis and 18 of 19 were treated with OK-432.[38] Of note, pleurodesis requires direct apposition of the visceral and parietal pleura.[39] Therefore, chemical pleurodesis should be performed only if there is no or only a small residual pneumothorax when the chest tube is placed on water seal. Otherwise, chemical pleurodesis should not be performed, as it may result in a lung that is unable to re-expand. Complications of chemical pleurodesis include chest pain, fever, acute lung injury, and empyema (incidence reported 1%).[6]

Autologous Blood Patch Pleurodesis

Autologous blood patch pleurodesis was first used by Robinson[40] in 1987 for the treatment of PALs. Since that time, there have been multiple case series as well as two randomized controlled trials documenting success. A recent review of 10 studies prior to 2010 found an overall success rate of 92% to 93% in patients with PALs following pulmonary resection or spontaneous pneumothorax.[41] Typically, 50 to 100 mL of peripheral venous blood is taken from the patient's arm and injected under sterile conditions through the chest tube into the pleural cavity.[42] The chest tube is then flushed with 10 mL of normal saline and either clamped or hooked over a drip stand so that air can escape, reducing the risk of tension physiology developing while allowing the blood to remain in the pleural space.[42] Reported complications are rare but include tension pneumothorax secondary to an obstructing clot in the chest tube, pleuritis, and empyema (incidence reported 0%-9%).[43]

Endobronchial/Intrabronchial Valves

Endobronchial valves (EBVs) and intrabronchial valves (IBVs) are one-way valves placed with a flexible bronchoscope in segmental or subsegmental bronchi to limit airflow to portions of the lungs distal to the placed valve while allowing mucous and air movement in the proximal direction. Both marketed devices (EBV: Zephyr, PulmonX Inc.; IBV: IBV/SVS system, Spiration, Inc.) have been approved by the US Food and Drug Administration for lung volume reduction in patients with emphysema. Most recently, the IBV/SVS system has been approved by the Food and Drug Administration through a humanitarian device exemption to treat PALs, reducing airflow across the fistula and allowing healing and resolution of the air leak.[44-46]

The placement process of an IBV is a series of steps aimed at identifying and occluding the lung segments contributing to the PAL. These steps include "air leak isolation, airway sizing, and valve deployment."[45] Leak isolation is achieved by sequential balloon occlusion of segmental airways, moving proximally to distally, starting at the mainstem bronchi. The IBV system comes with an airway sizing kit that calibrates the balloon catheter to measure the airway and determine the valve size. Once the valve is placed, the air leak chamber should be observed for four to five ventilatory cycles to assess any change in the degree of the air leak.[45] In prior studies, between one and 10 valves (mean of two to three) are typically required to control each PAL.[29,30]

Two case series by Travaline et al[29] and Gillespie et al[30] have detailed the use of EBVs and IBVs for PALs. Gillespie et al[30] described a series of seven patients with severe PALs that persisted for a median of 4 weeks after usual therapeutic measures failed. With IBV placement, the air leak improved in all patients and resulted in hospital discharge within 3 days in four of seven patients.[30] In a multicenter study with 40 patients, Travaline et al[29] showed the EBV Zephyr (PulmonX) to be an effective minimally invasive device for treating PALs. Following valve placement, the air leaks resolved or decreased in 37 patients (92.5%), with 19 patients (47.5%) having complete resolution of the air leak.[29] Six of 40 patients experienced complications, including valve malposition and expectoration, pneumonia, moderate oxygen desaturation, and methicillin-resistant *Staphylococcus aureus* colonization. A case series by Mahajan et al[47] documented the safety and success of IBVs for the treatment of PALs in patients in the ICU requiring high levels of oxygen or mechanical ventilation. A recent study by Reed et al[48] demonstrated the utility of IBVs in complex air leaks (including postoperative air leaks and those associated with cavitary infections), and a study by Toth et al[49] demonstrated the use of IBVs in air leaks in children.

A limitation of these five studies is the lack of a control group. Currently, the Valves Against Standard Therapy (VAST) study is ongoing. It is a multicenter prospective randomized controlled study designed to evaluate treatment of PALs with the IBV/SVS system (Spiration) compared with standard chest tube drainage management. This study is currently enrolling patients at multiple sites in the United States, with a goal enrollment of 200 patients.

Based on these case series as well as multiple case reports, placement of IBVs for PALs has been successful in some patients in whom conservative treatment has failed or who are poor surgical candidates.

Summary

Alveolar-pleural fistulas causing PALs are associated with prolonged hospital stays and high morbidity. Most recent guidelines recommend conservative watchful waiting with chest tube drainage followed by surgical repair as the gold standard for treatment. However, in patients who have recently undergone thoracic surgery or in whom surgery would be contraindicated based on the severity of illness, there has been a lack of effective treatment options. Proper chest tube management and ventilator management can help control many air leaks, and transition to an ambulatory drainage device (eg, Heimlich valve) can allow a leak to heal while avoiding the morbidity associated with prolonged hospitalization. Chemical or autologous blood patch pleurodesis and IBVs have been reported to be successful in resolving PALs in several case series.

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