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The Diagnosis and Management of Airway Complications Following Lung Transplantation

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Airway complications following lung transplantation result in considerable morbidity and are associated with a mortality of 2% to 4%. The incidence of lethal and nonlethal airway complications has decreased since the early experiences with double- and single-lung transplantation. The most common risk factor associated with post-lung transplantation airway complications is anastomotic ischemia. Airway complications include the development of exophytic granulation tissue, bronchial stenosis, bronchomalacia, airway fistula, endobronchial infection, and anastomotic dehiscence. The broadening array of bronchoscopic therapies has enhanced treatment options for lung transplant recipients with airway complications. This article reviews the risk factors, clinical manifestations, and treatments of airway complications following lung transplantation and provides our expert opinion when evidence is lacking.

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KEY WORDS: airway complications; bronchoscopy; lung transplantation

Since the advent of lung transplantation in the early 1960s, airway complications following surgery have resulted in appreciable morbidity and mortality.[1,2] Although advances in patient selection, organ preservation, surgical technique, immunosuppression, and postoperative intensive care have improved overall survival following lung transplantation, the mortality associated with post-lung transplantation airway complications remains between 2% and 4%.[3,4] Although this is a low attributable mortality, overall survival rates are reduced at 30 days, 90 days, 1 year, 3 years, and 5 years in lung transplant recipients experiencing airway complications.[5]

Common airway complications following lung transplantation include the development of excess granulation tissue, anastomotic stenosis, bronchomalacia, airway fistulas, anastomotic dehiscence, and airway infections. These airway complications are associated with significant functional impairment, poor quality of life, increased hospitalizations, and greater health-care resource use.[6,7] Despite

ABBREVIATIONS: BAR = bronchial artery revascularization; TBM = tracheobronchomalacia

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continued improvement in the care of lung transplantation patients, a paucity of data exists regarding transplantation-related airway complications. This review describes contemporary bronchoscopic techniques for treating airway complications following lung transplantation. We offer our expert opinion for treatment of each major category of airway complication in the hope of providing guidance for patient care and to drive future research.

Search Strategy and Selection Criteria

A peer-reviewed literature search was conducted to obtain published literature for this review. The following bibliographic databases were searched: Ovid MEDLINE with in-process records and daily updates through Ovid (1963 to present), including clinical trials and reviews. Search results included 591 publications. If objective data were not available, expert opinion was used. Keywords included airway complications and lung transplantation.

Incidence and Classification

The overall incidence of anastomotic airway complications following lung transplantation varies widely between 2% and 33% (Fig 1).[4,8] The incidence is similar to that of primary graft dysfunction, which is estimated to be between 10% and 25%, but significantly lower than chronic lung allograft dysfunction, which is estimated to be between 43% and 80%.[9-18] The lack of a universal classification system for describing airway complications following lung transplantation makes estimating the true incidence challenging. Although multiple classification systems for anastomotic complications have been proposed, such as those described by Couraud et al[19] and Shennib and Massard,[4] no classification scheme has been generally accepted by the transplantation community (Table 1). Couraud et al[19] classified airway healing by a grading system concerning the severity of airway necrosis. The classification of post-lung transplantation anastomotic

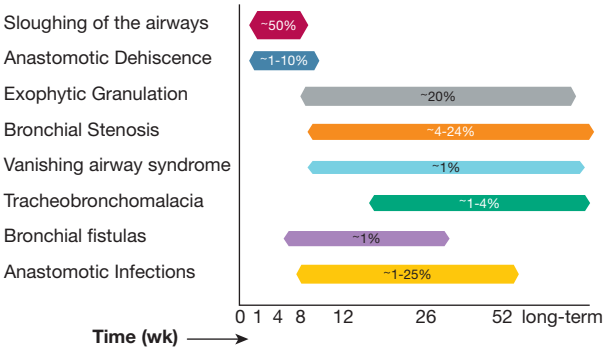

Figure 1 – *Conceptual depiction of the time to airway complications post-lung transplantation. Relative estimated incidence is represented by the vertical height of the respective bars. Time in weeks is represented on the horizontal axis.*

TABLE 1] Multiple Grading Systems for Bronchial Healing

Classification of Anastomotic Healing[a]
Grade 1: Complete primary mucosal healing
Grade 2A: Complete primary healing without necrosis—partial primary mucosal healing
Grade 2B: Complete primary healing without necrosis—no primary mucosal healing
Grade 3A: Limited focal necrosis (extending < 5 mm from the anastomotic line)
Grade 3B: Extensive necrosis
Uniform Reporting of the Airway Anastomosis[b]
1. No necrosis (primary healing mucosa to mucosa)
2. Ulceration or granulation
a. Mucosal ulceration (< 50% of circumference)
b. Mucosal ulceration (> 50% of circumference)
c. Mucosal granulation (< 50% narrowing of airway in diameter)
d. Mucosal granulation (> 50% narrowing of airway in diameter)
3. Partial-thickness necrosis
a. Submucosal and cartilage necrosis (< 50% of circumference)
b. Submucosal and cartilage necrosis (> 50% of circumference)
c. Healing by granulation (< 50% narrowing of diameter)
d. Healing by granulation (> 50% narrowing of diameter)
4. Full-thickness necrosis
a. Full-thickness necrosis (< 50% of circumference)
b. Full-thickness necrosis (> 50% of circumference)
c. Healing by granulation (<50% narrowing of diameter)
d. Healing by granulation (>50% narrowing of diameter)
5. Stricture and malacia
a. Fibrotic stricture (<50% narrowing of airway in diameter)
b. Fibrotic stricture (>50% narrowing of airway in diameter)
c. Anastomotic malacia (restricted to anastomosis and 1cm proximal and distal to it)
d. Diffuse malacia (involving all donor proximal airways)

[a]Adapted with permission from Couraud L, et al.[19]
[b]Adapted with permission from Shennib H, Massard G.[4]

healing in their cohort revealed 18% grade 1, 54% grade 2, and 28% grade 3. A favorable prognosis without long-term complications was reported with grade 1 and 2 lesions, whereas grade 3 lesions were associated with a higher risk for airway complications.[19] Shennib and Massard[4] also proposed a detailed classification for airway and anastomotic complications incorporating variable degrees of healing, which has also gained favor by many physicians.

Risk Factors

Anastomotic Ischemia

The development of airway complications following lung transplantation is likely driven by the absence of systemic blood supply to the anastomotic region following surgery. Normal lungs and airways benefit from a dual blood supply arising from the pulmonary arteries as well as the bronchial arteries. During lung transplantation, the bronchial arterial blood supply is not typically reconstructed. It may take up to 4 weeks before the bronchial artery circulation is re-established through collateral formation.[20,21] As a result, the donor bronchus is susceptible to ischemic injury during this period. The resulting necrosis incites an inflammatory cascade, with associated bronchial lumen remodeling and an increased likelihood of airway complications (Fig 2). We favor avoiding low cardiac output, hypotension, and dehydration in the weeks following transplantation, as these factors may further decrease the blood supply to the anastomosis and increase the risk of ischemia. Direct bronchial artery revascularization (BAR) is a technique that aims to re-establish bronchial artery circulation during lung transplantation. Comparable early outcomes with and without BAR have been reported regarding the development of airway complications. Given the complexity of the procedure and equivalent outcomes, BAR is not routinely performed. Additionally, the potential for increased graft ischemic time and the possible need for cardiopulmonary bypass during BAR offsets possible benefits.

Surgical Technique

Multiple surgical options exist for anastomosing the donor and recipient bronchi during lung transplantation. The most commonly used surgical techniques include the "end-to-end" and "telescoping" anastomoses. The end-to-end anastomosis is accomplished by direct attachment of the donor bronchus to the recipient bronchus without overlapping of tissue (Fig 3).[22] Telescoping anastomosis involves overlapping the donor and recipient bronchi. This technique may become necessary when there is a significant difference between the airway diameters of the donor and the recipient. Telescoping anastomoses are associated with a 48% incidence of airway complications, specifically anastomotic stenosis and infection.[22]

The length of the donor bronchus can significantly influence the development of airway ischemia. Anastomosing a short donor bronchus with a longer recipient bronchus may reduce the risk of prolonged ischemia due to the decreased length needed for collateral circulation formation.[23] In one study of 65 pediatric patients, shortening the donor bronchus length by dividing it at the lobar carina resulted in a reduction in airway complications in the first year

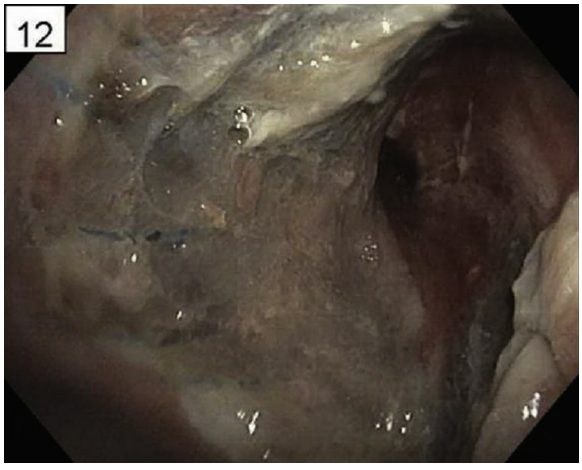

Figure 2 – *Ischemic changes of the right main stem anastomosis 2 weeks following lung transplantation.*

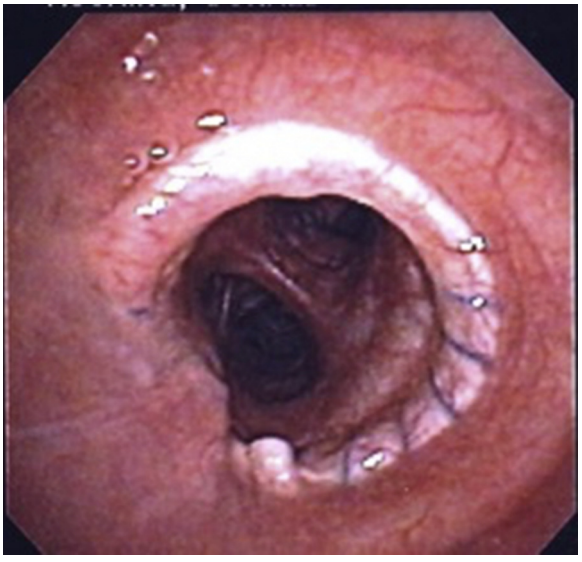

Figure 3 – *Normal end-to-end right-sided anastomosis 3 months following transplantation.*

following lung transplantation vs the standard technique (2.6% vs 11.1%).[23]

Pulmonary Infection

The presence of particular preoperative and postoperative pulmonary infections increases the incidence of transplantation-related airway complications. Preoperative infection with *Pseudomonas cepacia* was a risk factor for airway complications when accounting for other covariates in a single-institution study of 214 pediatric patients who had undergone lung transplantation. The relative risk of an airway complication developing in patients with preoperative *P cepacia* infection was 29% greater than in uninfected patients (95% CI, 2.84-303.26; $P = .002$).[23] Postoperative fungal infections, specifically isolation of *Aspergillus fumigatus*, have also been shown to have a strong association with the development of airway complications when identified in the first 30 days following transplantation.[24]

Allograft Dysfunction and Rejection

In the immediate postoperative period, ischemia reperfusion injury was associated with bronchial complications in a cohort of 81 lung recipients from a single center.[25] Additionally, development of rejection in the first month following transplantation may also be associated with an increased risk of bronchial complications.[26] Furthermore, a study by Castleberry et al[26] reviewing 9,335 patients found a significant association of bronchial strictures with the presence of acute rejection in the first postoperative year. Studies such as these lead us to believe that some correlation exists between allograft rejection and airway complications, but further trials are needed to solidify the association.

Management of Airway Complications

Exophytic Granulation Tissue

The development of obstructive granulation tissue can result in significant airway obstruction within a few months of surgery in up to 20% of patients undergoing lung transplantation (Fig 4).[27] The presence of *Aspergillus* infection at the surgical anastomosis may exacerbate the development of granulation tissue and result in recurrent obstruction.[28] Airway debridement is the standard practice for the removal of granulation tissue at the surgical anastomosis.

Our consensus opinion regarding the treatment of anastomotic granulation tissue depends on whether the pattern of growth is obstructive or nonobstructive. We favor the use of flexible or rigid forceps for debridement of nonobstructive granulation tissue that is eccentric in nature.[29] Flexible forceps allow for precise debridement, whereas rigid forceps can be used for bulkier areas of granulation tissue. Obstructive granulation tissue resulting in airway compromise is best treated with cold therapies, including cryodebridement or cryotherapy. Cryodebridement can be performed using the cryotherapy probe to freeze granulation tissue, followed by withdrawal of the probe with the tissue attached.[30] Cryotherapy, in contrast, involves repeated cycles of freezing and thawing of obstructing tissue. This process crystallizes tissue, causing microthrombi formation along with intracellular and extracellular ice crystal formation resulting in cell death.[31,32] In the weeks following cryotherapy, necrosing granulation tissue sloughs off the airway without damage to the bronchial wall. Cryodebridement and cryotherapy are effective in recanalizing the airway without inciting further inflammation. Hot therapies, such as Nd:YAG laser, argon plasma coagulation, or electrocautery, are also effective in restoring patency to airways, but they harbor the potential for generating further inflammation and provoking more granulation tissue formation. Instead, these hot therapies are typically reserved to control bleeding following treatment with cryodebridement or cryotherapy.

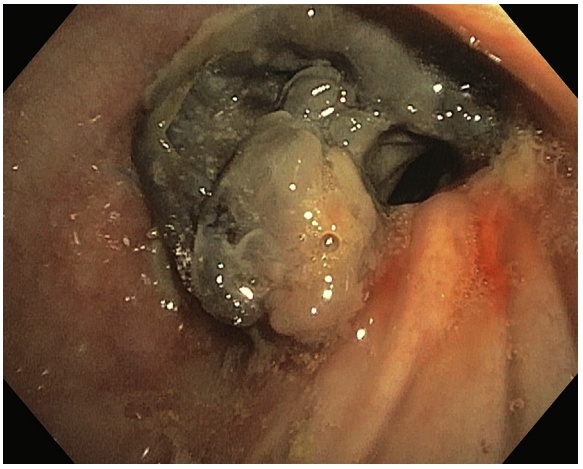

Figure 4 – *Exophytic granulation with airway obstruction.*

Additional experimental therapies for the treatment of granulation tissue formation include topical mitomycin C and high-dose endobronchial brachytherapy. Topical mitomycin C is an antineoplastic agent that can halt fibroblast proliferation. The use of topical mitomycin C after debridement has been demonstrated to reduce

granulation tissue recurrence in patients who have undergone lung transplantation.[33] Endobronchial brachytherapy also slows fibroblast proliferation by concentrating radiation within the airways without affecting surrounding structures.[34] Although we consider these modalities to have great potential, randomized controlled trials are needed to validate sustained efficacy and safety.

Bronchial Stenosis

Bronchial stenosis is the most common airway complication following lung transplantation. The incidence of bronchial stenosis is 4% to 24% and typically occurs within 2 to 9 months of transplantation.[35-39] The presence of bronchial stenosis has been shown to be an independent risk factor for death after adjusting for confounders (adjusted hazard ratio, 1.13; 95% CI, 1.03-1.23; $P = .007$).[26] Although bronchial ischemia is a well-known risk factor for anastomotic stenosis, severe reperfusion edema and early rejection have also been shown to be independent risk factors.[25,26] CT imaging may be sensitive in identifying bronchial stenosis, but bronchoscopy remains the gold standard for diagnosis.

Two patterns of airway stenosis have been described following lung transplantation: anastomotic stenosis and nonanastomotic stenosis. Stenosis at the anastomosis is more common in patients in whom anastomotic necrosis, infection, or dehiscence has developed (Fig 5). Nonanastomotic stenosis occurs less commonly and develops distal to the anastomosis.

Traditionally, the initial treatment of anastomotic and nonanastomotic stenoses involves balloon bronchoplasty. A controlled radial expansion balloon can be used to dilate the stenosis to a specific diameter, with multiple inflations held for 30 to 60 s, with or without fluoroscopic guidance. Balloon bronchoplasty may be the only procedure required in up to 26% of patients with bronchial stenosis.[40] Although we agree that balloon bronchoplasty may be effective in mild weblike stenoses by providing an immediate increase in airway diameter, the symptomatic improvements are often short lived. Because balloon bronchoplasty stretches the airway circumferentially, the airway often returns to the original narrowed state over time. Instead, we recommend combining balloon bronchoplasty with radial incisions and steroid injections at the site of stenosis. Radial incisions allow tearing along the radial scores during dilation rather than mere circumferential stretching of the airway. Incisions are traditionally made at the 12 o'clock, 8 o'clock, and 4 o'clock positions with an electrocautery knife or Nd:YAG laser. Injection of corticosteroids into the airway mucosa using a Wang needle at the sites of radial incisions may reduce inflammation and prevent restenosis.[41]

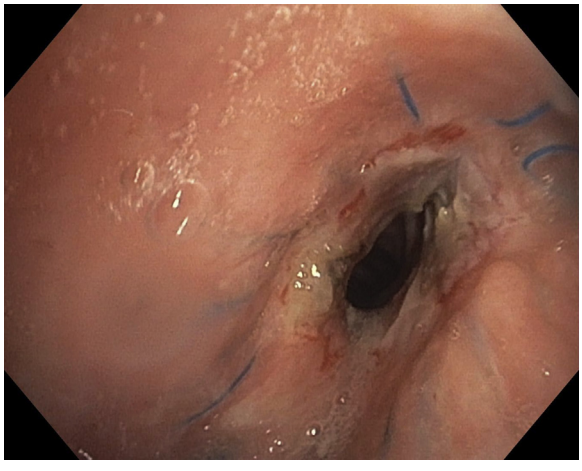

Figure 5 – *Stenosis of the right-sided anastomosis.*

Severe bronchial stenoses refractory to balloon bronchoplasty combined with radial incisions and steroid injections require stent placement (Fig 6). One study featuring 41 patients with bronchial stenosis demonstrated a mean survival of 82 months vs 22 months, respectively, in patients undergoing stent placement compared with those who underwent simple bronchoplasty.[42] We prefer the use of silicone stents for airway stenosis following lung transplantation. Depending on the location and specific contour of the stenosis, a tubular or customized silicone stent can be used. Silicone Y stents are comprised of a tracheal limb along with two bronchial limbs and can be used in stenoses proximal to the main carina or in situations in which bilateral main stem stenoses are present. The ultimate goal of silicone stent placement is to restore airway diameter and allow for airway remodeling by using the body's propensity to granulate. Although we agree that careful bronchoscopic surveillance of silicone stents is recommended every 4 to 6 weeks, no consensus exists on the duration of time that silicone stents should remain in the airways. The duration for stent placement ranges anywhere from 2 months to 1 year. The interval of time a stent should remain in the airways deserves further research with randomized controlled studies. In situations in which a silicone stent cannot easily be placed due to severe stenosis, self-expanding metallic stents can be used to dilate the airway serially until a long-term silicone stent can be

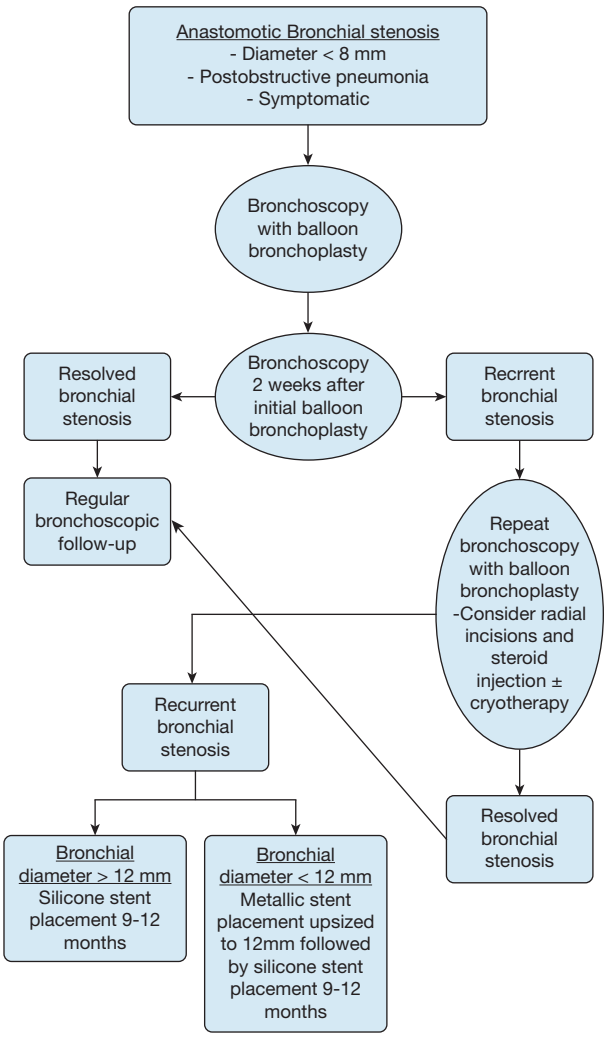

Figure 6 – *Treatment algorithm for patients with bronchial stenosis.*

placed (Fig 7). Although we agree that self-expanding metallic stents are effective in the treatment of severe anastomotic stenosis, they should be removed within 4 to 6 weeks of placement due to the potential for excessive granulation tissue formation, which can make stent extraction challenging.

Stent migration and granulation tissue formation are potential complications of stent placement and must be considered, particularly when using self-expanding metallic stents. A retrospective study of 17 cases demonstrated subjective and objective (FEV_1) improvement following stent placement, with a complication rate of only 0.13 per patient per month.[35] The development of biodegradable stents has sparked interest in the treatment of airway stenosis, as they can absorb over time and are associated with a reduced risk of granulation tissue formation. Small studies featuring the use of biodegradable stents show their promise as treatment options to overcome the limitation of current stent designs.[43]

A small subset of refractory bronchial stenosis cases requires surgical intervention. Such treatments include anastomotic reconstruction, sleeve resection with and without lobar resection, and rarely retransplantation.[44] Repeated lung transplantation accounts for 2% of all transplantations worldwide, but very few are performed for refractory airway complications. Therefore, a paucity of data on operative strategies and outcomes exists for this subgroup of patients undergoing retransplantation for airway complications.[45]

Transplantation-Related Bronchomalacia

Bronchomalacia describes pathologic weakness of bronchial walls leading to an accentuation of normal airway narrowing on expiration. Although there is no definite consensus on the degree of narrowing that is considered pathologic, a criterion of > a 50% decrease in the luminal diameter on expiration has been widely accepted for the diagnosis of bronchomalacia (Fig 8).[46,47]

The incidence of bronchomalacia following lung transplantation is not well documented, but a single-center study describes an incidence of approximately 1% to 4%.[48] In patients who have undergone lung transplantation, bronchomalacia can be classified as either perianastomotic bronchomalacia or distal malacia. The former is found 1 cm proximal or distal to the bronchial anastomosis, whereas the latter is located more distally.

The mechanism underlying bronchomalacia in patients who have undergone lung transplantation is not well understood but has been associated with the presence of bronchiolitis obliterans.[49] In patients with tracheobronchomalacia (TBM) who have not undergone lung transplantation, autopsy studies have shown atrophy and reduction in the number of the longitudinal elastic fibers of the pars membranacea and "fragmentation" of the tracheal cartilage.[50,51] It is unclear if similar pathologic changes are present in patients who have undergone transplantation and have the diffuse form of bronchomalacia.

Perianastomotic malacia typically presents within 4 months of transplantation. Symptoms are similar to those in patients who have not undergone transplantation and include cough, wheezing, dyspnea, sputum production, and recurrent respiratory

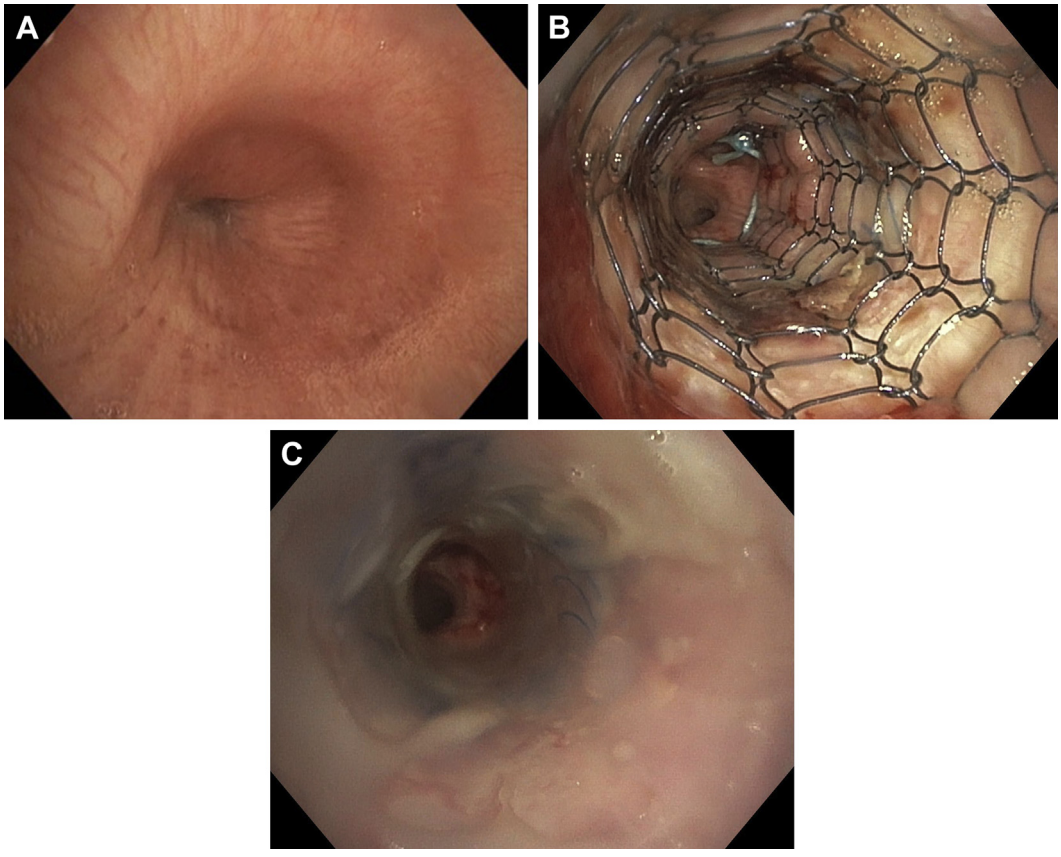

Figure 7 – *A, Anastomotic stenosis 3 weeks after lung transplantation. B, The same anastomotic stenosis is featured; it required initial treatment with a metallic uncovered stent because a silicone stent could not pass through the narrowed opening. C, The same anastomotic stenosis after replacing metallic stent with silicone stent.*

infections. Some patients may remain asymptomatic until a supervening secondary factor manifests, such as the development of infection or rejection.

The current gold standard for the diagnosis of airway malacia, both transplantation and nontransplantation related, is bronchoscopic visualization of the airway during forced expiration.[52] Numerous studies have assessed the utility of multidetector CT imaging in the diagnosis of TBM, but none has proved as sensitive as flexible bronchoscopy.[46] Majid et al[53] proposed a structured approach to assess the location and degree of expiratory collapse during flexible bronchoscopy using dynamic airway maneuvers for nontransplantation TBM. These maneuvers are performed with the patient under light sedation and require the patient to inhale and forcibly exhale when instructed. Based on the study by Majid et al,[53] visualization of posterior tracheal membrane bowing resulting in a $>$ 50% reduction in airway diameter on forced expiration is associated with clinically relevant TBM that is often manifested by shortness of breath.

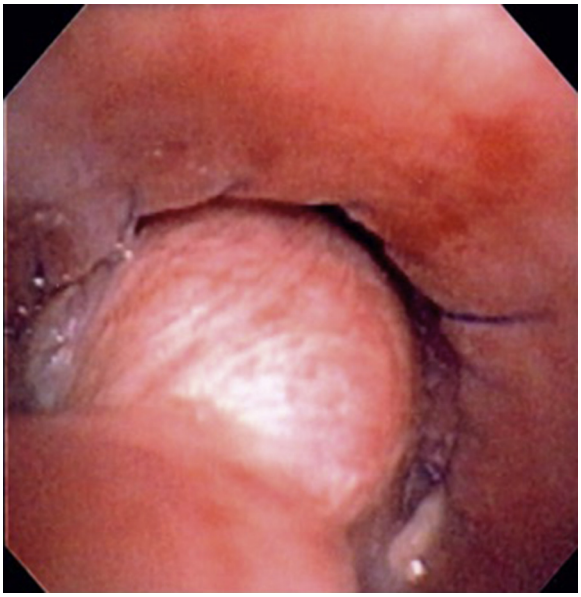

Figure 8 – *Right main stem anastomosis with severe malacia on exhalation.*

We consider the management of transplant-related bronchomalacia to mirror that of non-transplant-related malacia (Fig 9). The decision to treat bronchomalacia depends on the severity of symptoms and the extent of airway collapse. Asymptomatic patients with mild disease may not require treatment but warrant continued observation. In patients with moderate collapse and functional impairment, treatment options include pulmonary hygiene, mucolytic agents, and noninvasive positive-pressure ventilation.

If the degree of malacia is severe, with functional impairment despite conservative medical therapy, we favor silicone stent placement. Silicone stents rapidly establish and maintain the patency of malacic airway segments during expiration. We recommend 9 to 12 months of in situ silicone stent placement to allow for adequate airway remodeling. If the location of the malacic segment and shape of the airway is not conducive to silicone stent placement, self-expanding metallic stents may provide better palliation.[54,55] We believe that the optimal duration of self-expanding metallic stent placement for malacia should be 4 to 6 weeks to avoid excessive granulation formation. Because of expected scarring following lung transplantation, surgical intervention for posttransplantation bronchomalacia would be extremely challenging and is not recommended.

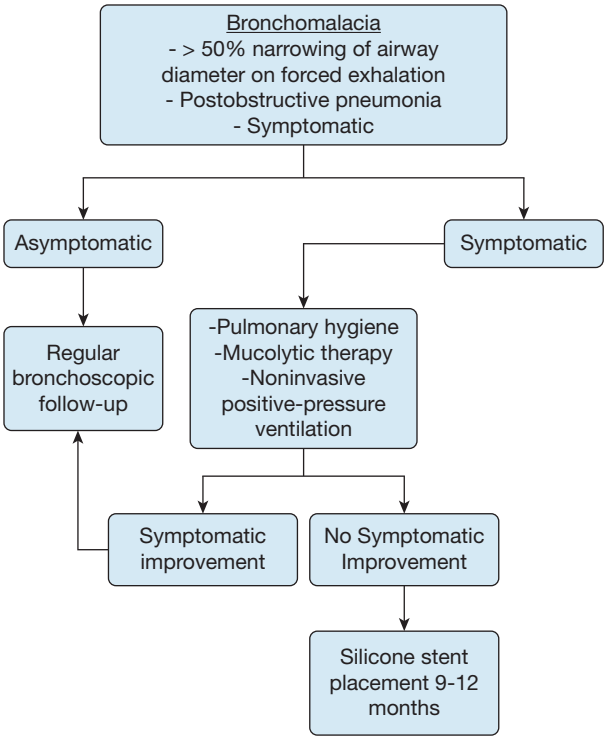

Figure 9 – *Treatment algorithm for patients with bronchomalacia.*

Bronchial Fistulas

Bronchopleural fistulas are pathologic communications between the bronchial wall and surrounding structures usually due to prolonged or profound ischemia (Fig 10).[56] Clinical manifestations include dyspnea, hypotension, subcutaneous emphysema, pneumothorax, and a persistent air leak.[57,58] Source control, attained through tube thoracostomy of any associated empyema, along with broad-spectrum antibiotics, including anaerobic coverage, is the first step in the management of bronchopleural fistulas. In intubated patients, limiting airflow through the defect with low-tidal-volume ventilation and minimal positive end-expiratory pressure can expedite healing. Surgical options in appropriate patients include chronic open drainage, direct closure with flap reinforcement, transsternal bronchial closure, or thoracoplasty.[56] We believe that patients not deemed candidates for surgical closure should be treated endoscopically with fibrin glue for bronchopleural fistulas measuring 3 to 5 mm or metallic stent placement to cover more proximal large fistulas.

Bronchomediastinal fistulas typically present with mediastinal infection along with constitutional symptoms consistent with the systemic inflammatory response syndrome. We believe that small fistulas should be treated with aerosolized antibiotic therapy along with

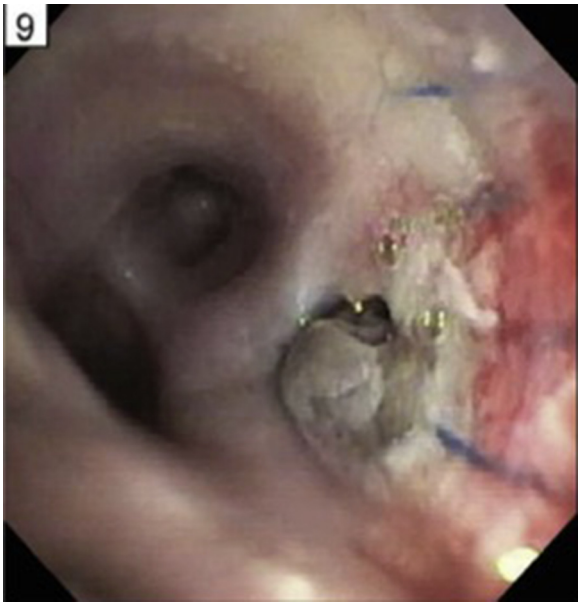

Figure 10 – *Bronchomediastinal fistula at left-sided anastomosis 6 weeks after lung transplantation.*

percutaneous drainage. Depending on the severity and extent of infection, mediastinal debridement may be indicated.

The development of a bronchovascular fistula is rare but is associated with high mortality. Fistula formation between the bronchus and the pulmonary artery, pulmonary vein, aorta, or left atrium typically manifests as hemoptysis followed by massive hemorrhage and sudden death.[59] Few therapeutic interventions are effective for the treatment of bronchovascular fistulas. Successful management with lobectomy and pneumonectomy has been reported in individual cases.[60,61]

Anastomotic Dehiscence

Anastomotic dehiscence is a complication of lung transplantation that is associated with high morbidity and mortality.[62,63] Dehiscence is thought to result from extreme mucosal necrosis with separation of the surgical anastomosis.[37,64-66] One case series reported some degree of dehiscence, including clinically insignificant cases, in up to 24% of patients.[22] Fortunately, severe dehiscence is rare, with an estimated incidence of less than 2%.[67]

The risk factors for dehiscence are similar to those of other airway complications, including ischemia, surgical technique, high doses of perioperative steroids, acute rejection, infection, inadequate organ preservation, and immunosuppression.[19,25,36,65,67,68] A strong correlation between culture-proven *Aspergillus* colonization, even in the absence of active infection, and bronchial wall necrosis has been described.[24,36] The use of sirolimus, a rapamycin derivate, has also been associated with a high incidence of dehiscence if used early in the postoperative period.[69]

Common presenting symptoms of anastomotic dehiscence include dyspnea, subcutaneous emphysema, pneumothorax, an inability to wean from mechanical ventilation, pneumomediastinum, or a persistent air leak in the early posttransplantation period. Other patients may present with infection and rapidly progressive sepsis.

Bronchoscopy is required to diagnose and adequately assess the severity of anastomotic dehiscence. A CT scan of the chest is a noninvasive modality for detection of airway dehiscence based on the test's high sensitivity and specificity, but bronchoscopy is essential for diagnosis.[70] Our approach for the management of anastomotic dehiscence depends on the symptoms and the severity. Partial dehiscence is often treated conservatively with close bronchoscopic surveillance along with antibiotic therapy, both IV and inhaled.[67] Bronchoscopic therapies for severe dehiscence include the use of stents, cyanoacrylate glue, growth factors, and autologous platelet-derived wound-healing factor.[62,71] Successful management of severe dehiscence has been reported with the temporary placement of uncovered self-expanding metallic stents.[67,72] We agree with the use of uncovered self-expanding metallic stents for the treatment of clinically significant dehiscence. The known adverse effect of excessive granulation tissue formation associated with self-expanding metallic stents is used to provide a platform for dehiscence healing and remodeling of the airway. We prefer uncovered self-expanding metallic stents to avoid bacterial colonization of the stent coating and to allow drainage of mediastinal and bronchial secretions while still allowing ventilation of involved lobes. Typically, self-expanding metallic stents are removed after 4 to 6 weeks to avoid excess growth of granulation tissue, which would making stent removal challenging. Extreme caution is required for the deployment and removal of self-expanding metallic stents due to the risk of creating a larger defect with stent manipulation.

Surgical treatment options for anastomotic dehiscence include open repair for reanastomosis, flap bronchoplasty, transplant pneumonectomy, or retransplantation.[36] Typically, surgical repair is reserved for severe cases or complete dehiscence. These surgical procedures are extremely risky and generally yield poor outcomes.[65]

Anastomotic Infections

The combination of immunosuppression along with allograft exposure to the external environment increases the risk of opportunistic infections following lung transplantation. The bronchial anastomosis is particularly susceptible to saprophytic infections due to devascularization following transplantation, defense impairment (ie, mucociliary clearance and cough reflex), disruption of lymphatic drainage, and altered alveolar phagocytic function.[73] *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the most common bacterial infections following lung transplantation and may manifest as tracheitis, bronchitis, or pneumonia. Fungal infections occur in 15% to 35% of recipients after lung transplantation; *Aspergillus* species together with *Candida* species are responsible for $>$ 80% of these infections.[74]

Effective strategies to prevent and counter posttransplantation infections include antifungal prophylaxis along with aggressive and early treatment with broad-spectrum therapy for organisms detected on bronchoscopy. A worldwide survey of 43 lung transplantation centers in 2002 revealed a practice of universal antifungal prophylaxis in the postoperative period in 69% of the centers, whereas 31% used aggressive treatment of fungal airway colonization, even in the absence of active infection.

We acknowledge that differentiating anastomotic infection from colonization can be difficult in the post-lung transplantation population. Isolation of bacterial or fungal species should be based on biopsy samples obtained directly from the anastomosis. Further evidence supporting the use of antibiotics includes systemic symptoms of infection and the presence of anastomotic erythema or pseudomembrane formation.

Conclusions

Airway complications represent a significant source of morbidity and potential mortality in lung transplant recipients. Although the incidence of airway complications is significantly lower than other more common transplantation-related maladies such as chronic lung allograft dysfunction, they often represent a management conundrum for clinicians when they do supervene. Patients may be beset by recurrent hospitalizations and repeated procedures, which may profoundly affect the quality of life. Despite significant progress in surgical technique, immunosuppressive strategies, and postoperative intensive care, the optimal management of airway complications post-lung transplantation has yet to be clearly defined. Myriad questions remain regarding the best approach to treat airway complications, providing fertile ground for future research (Table 2). Indeed, transplant physicians and interventional pulmonologists should focus jointly on high-quality research to avert and treat airway complications, thus improving the quality of life and survival of the growing population of lung transplant recipients.

TABLE 2] Airway Complications Post-Lung Transplantation: Topics for Future Research

1. Determine the role of mitomycin C and brachytherapy in the treatment of granulation tissue and anastomotic stenosis
2. What is the role of balloon bronchoplasty with balloons coated with a chemotherapeutic agent?
3. Is there a role for biodegradable stents in anastomotic stenosis and bronchomalacia?
4. What are the health-care costs associated with airway complications following lung transplantation?

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References

1. Wildevuur CRH, Benfield JR. A review of 23 human lung transplantations by 20 surgeons. *Ann Thorac Surg*. 1970;9(6):489-515.
2. Derom F, Barbier F, Ringoir S, et al. Ten-month survival after lung homotransplantation in man. *J Thorac Cardiovasc Surg*. 1971;61(6):835-846.
3. Date H, Trulock EP, Arcidi JM, Sundaresan S, Cooper JD, Patterson GA. Improved airway healing after lung transplantation. An analysis of 348 bronchial anastomoses. *J Thorac Cardiovasc Surg*. 1995;110(5):1424-1432; discussion 32-33.
4. Shennib H, Massard G. Airway complications in lung transplantation. *Ann Thorac Surg*. 1994;57(2):506-511.
5. Awori Hayanga JW, Aboagye JK, Shigemura N, et al. Airway complications after lung transplantation: contemporary survival and outcomes. *J Heart Lung Transplant*. 2016;35(10):1206-1211.
6. Dezfouli AA, Najafizadeh K, Parsa T, et al. Postlung transplant rehospitalization: a study of causes, health care burden, and outcomes. *Exp Clin Transplant*. 2009;7(3):192-196.
7. Seiler A, Jenewein J, Martin-Soelch C, et al. Post-transplant outcome-clusters of psychological distress and health-related quality of life in lung transplant recipients. *Swiss Med Wkly*. 2015;145:w14236.
8. Van De Wauwer C, Van Raemdonck D, Verleden GM, et al. Risk factors for airway complications within the first year after lung transplantation. *Eur J Cardiothoracic Surg*. 2007;31(4):703-710.
9. Christie JD, Edwards LB, Aurora P, et al. The registry of the International Society for Heart and Lung Transplantation: twenty-sixth official adult lung and heart-lung transplantation report-2009. *J Heart Lung Transplant*. 2009;28(10):1031-1049.
10. Christie JD, Bavaria JE, Palevsky HI, et al. Primary graft failure following lung transplantation. *Chest*. 1998;114(1):51-60.
11. Christie JD, Kotloff RM, Pochettino A, et al. Clinical risk factors for primary graft failure following lung transplantation. *Chest*. 2003;124(4):1232-1241.
12. King RC, Binns OA, Rodriguez F, et al. Reperfusion injury significantly impacts clinical outcome after pulmonary transplantation. *Ann Thorac Surg*. 2000;69(6):1681-1685.
13. Christie JD, Sager JS, Kimmel SE, et al. Impact of primary graft failure on outcomes following lung transplantation. *Chest*. 2005;127(1):161-165.
14. Khan SU, Salloum J, O'Donovan PB, et al. Acute pulmonary edema after lung transplantation: the pulmonary reimplantation response. *Chest*. 1999;116(1):187-194.
15. Verleden GM, Dupont LJ, Van Raemdonck DE. Is it bronchiolitis obliterans syndrome or is it chronic rejection: a reappraisal? *Eur Respir J*. 2005;25(2):221-224.
16. Burton CM, Carlsen J, Mortensen J, Andersen CB, Milman N, Iversen M. Long-term survival after lung transplantation depends on development and severity of bronchiolitis obliterans syndrome. *J Heart Lung Transplant*. 2007;26(7):681-686.
17. Heng D, Sharples LD, McNeil K, Stewart S, Wreghitt T, Wallwork J. Bronchiolitis obliterans syndrome: incidence, natural history, prognosis, and risk factors. *J Heart Lung Transplant*. 1998;17(12):1255-1263.
18. Trulock EP, Christie JD, Edwards LB, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-fourth official

adult lung and heart-lung transplantation report-2007. *J Heart Lung Transplant*. 2007;26(8):782-795.

19. Couraud L, Nashef SA, Nicolini P, et al. Classification of airway anastomotic healing. *Eur J Cardiothorac Surg*. 1992;6(9):496-497.
20. Pearson FG, Goldberg M, Stone RM, et al. Bronchial arterial circulation restored after reimplantation of canine lung. *Can J Surg*. 1970;13(3):243-250.
21. Siegelman SS, Hagstrom JW, Koemer SK, et al. Restoration of bronchial artery circulation after canine lung allotrasplantation. *J Thorac Cardiovasc Surg*. 1977;73(5):792-795.
22. Garfein ES, McGregor CC, Galantowicz ME, Schulman LL. Deleterious effects of telescoped bronchial anastomosis in single and bilateral lung transplantation. *Ann Transplant*. 2000;5(1):5-11.
23. Choong CK, Sweet SC, Zoole JB, et al. Bronchial airway anastomotic complications after pediatric lung transplantation: incidence, cause, management, and outcome. *J Thorac Cardiovasc Surg*. 2006;131: 198-203.
24. Herrera JM, McNeil KD, Higgins RS, et al. Airway complications after lung transplantation: treatment and long-term outcomes. *Ann Thorac Surg*. 2001;71(3):993-994.
25. Ruttman E, Ulmer H, Marchese M, et al. Evaluation of factor damaging the bronchial wall in lung transplantation. *J Heart Lung Transplant*. 2005;24(3):275-285.
26. Castleberry AW, Worni M, Kuchibhatia M, et al. A comparative analysis of bronchial stricture after lung transplant in recipients with and without early acute rejection. *Ann Thorac Surg*. 2013;96(3): 1008-1017.
27. Tendulkar RD, Fleming PA, Reddy CA, Gildea TR, Machuzak M, Mehta AC. High-dose-rate endobronchial brachytherapy for recurrent airway obstruction from hyperplastic granulation tissue. *Int J Radiat Oncol Biol Phys*. 2008;70(3):701-706.
28. Nathan SD, Shorr AF, Schmidt ME, Burton NA. Aspergillus and endobronchial abnormalities in lung transplant recipients. *Chest*. 2000;118(2):403-407.
29. Kaditis AG, Gondor M, Nixon PA, et al. Airway complications following pediatric lung and heart-lung transplantation. *Am J Respir Crit Care Med*. 2000;162(1):301-309.
30. Inaty H, Folch E, Fernandez-Bussy S, et al. Cryodebridement for airway obstruction: a retrospective outcome and safety analysis. *Chest*. 2013;144(4_meeting abstract):809A.
31. Mathur PN, Wolf KM, Busk MF, Briete WM, Datzman M. Fiberoptic bronchoscopic cryotherapy in the management of tracheobronchial obstruction. *Chest*. 1996;110(3):718-723.
32. Fernando HC, Dekeratry D, Downie G, et al. Feasability of spray cryotherapy and balloon dilation for non-malignant strictures of airway. *Eur J Cardiothorac Surg*. 2011;40(5):1177-1180.
33. Erard AC, Monnier P, Spiliopoulos A, Nicod L. Mitomycin C for control of recurrent bronchial stenosis: a case report. *Chest*. 2001;120(6):2103-2105.
34. Halkos ME, Godette KD, Lawrence EC, Miller JI Jr. High dose rate brachytherapy the management of lung transplant airway stenosis. *Ann Thorac Surg*. 2003;76(2):381-384.
35. Dutau H, Cavailles A, Sakr L, Badier M, et al. A retrospective study of silicone stent placement for management of anastomotic airway complications in lung transplant recipients: short- and long-term outcomes. *J Heart Lung Transplant*. 2010;29(6):658-664.
36. Moreno P, Alvarez A, Algar FJ, et al. Incidence, management and clinical outcomes of patients with airway complications following lung transplantation. *Eur J Cardiothorac Surg*. 2008;34(6): 1198-1125.
37. Weder W, Inci I, Korom S, et al. Airway complications after lung transplantation: risk factors, prevention and outcome. *Eur J Cardiothorac Surg*. 2009;35(2):293-298.
38. Hasegawa T, Iacono AT, Orons PD, et al. Segmental nonanastomotic bronchial stenosis after lung transplantation. *Ann Thorac Surg*. 2000;69(4):1020-1024.
39. De Gracia J, Culebras M, Alvarez A, et al. Bronchoscopic balloon dilatation in the management of bronchial stenosis following lung transplantation. *Respir Med*. 2007;101(1):27-33.
40. Chhajed PN, Malouf MA, Tamm M, et al. Ultraflex stents for the management of airway complications in lung transplant recipients. *Respirology*. 2003;8(1):59-64.
41. Tremblay A, Coulter TD, Mehta AC. Modification of a mucosal-sparing technique using electrocautery and balloon dilatation in the endoscopic management of web-like benign airway stenosis. *J Bronchol*. 2003;10:268-271.
42. Abi-Jaoudeh N, Francois RJ, Oliva VL, et al. Endobronchial dilation for the management of bronchial stenosis in patients after lung transplantation: effect of stent placement on survival. *J Vasc Interv Radiol*. 2009;20(7):912-920.
43. Fuehner T, Suhling H, Greer M, et al. Biodegradable stents after lung transplantation. *Transpl Int*. 2013;26(7):e58-e60.
44. Marulli G, Loy M, Rizzardi G, et al. Surgical treatment of posttransplant bronchial stenoses: case reports. *Transplant Proc*. 2007;39(6):1973-1975.
45. Mulligan MS. Endoscopic management of airway complications after lung transplantation. *Chest Surg Clin N Am*. 2001;11(4):907-915.
46. Ridge CA, O'Donnell CR, Lee EY, Majid A, Boiselle PM. Tracheobronchomalacia: current concepts and controversies. *J Thorac Imaging*. 2011;26(4):278-289.
47. Boiselle PM, Feller-Kopman D, Ashiku S, Weeks D, Ernst A. Tracheobronchomalacia: evolving role of dynamic multislice helical CT. *Radiol Clin North Am*. 2003;41(3):627-636.
48. Simoff MJ, Sterman DH, Ernst A, eds. *Thoracic Endoscopy Advances in Interventional Pulmonology*. Malden, MA: Blackwell Publishing; 2006.
49. Novick RJ, Ahmad D, Menkis AH, et al. The importance of acquired diffuse bronchomalacia in heart-lung transplant recipients with obliterative bronchiolitis. *J Thorac Cardiovasc Surg*. 1991;101(4): 643-648.
50. Ikeda S, Hanawa T, Konishi T, et al. Diagnosis, incidence, clinicopathology and surgical treatment of acquired tracheobronchomalacia. *Nihon Kyobu Shikkan Gakkai Zasshi*. 1992;30(6):1028-1035.
51. Jokinen K, Palva T, Sutinen S, Nuutinen J. Acquired trachobron-chomalacia. *Ann Clin Res*. 1977;9(2):52-57.
52. Carden KA, Boiselle PM, Waltz DA, Ernst A. Tracheomalacia and tracheobronchomalacia in children and adults. *Chest*. 2005;127(3): 984-1005.
53. Majid A, Gaurav K, Sanchez JM, et al. Evaluation of tracheobronchomalacia by dynamic flexible bronchoscopy: a pilot study. *Ann Am Thorac Soc*. 2014;11(6):951-955.
54. Susanto I, Peters JI, Levine SM, Sako EY, Anzueto A, Bryan CL. Use of balloon-expandable metallic stents in the management of bronchial stenosis and bronchomalacia after lung transplantation. *Chest*. 1998;114(5):1330-1335.
55. Bolot G, Poupart M, Pignat JC, et al. Self-expanding metal stents for the management of bronchial stenosis and bronchomalacia after lung transplantation. *Laryngoscope*. 1998;108(8 pt 1):1230-1233.
56. Chang CC, Hsu HH, Kuo SW, Lee YC. Bronchoscopic gluing for post-lung-transplant bronchopleural fistula. *Eur J Cardiothorac Surg*. 2007;31(2):328-330.
57. Lois M, Noppen M. Bronchopleural fistulas: an overview of the problem with special focus on endoscopic management. *Chest*. 2005;128(6):3955-3965.
58. Mora G, de Pablo A, Garcia-Gallo CL, et al. Is endoscopic treatment of bronchopleural fistula useful [in Spanish]? *Arch Bronconeumol*. 2006;42(8):394-398.
59. Hoff SJ, Johnson JE, Frist WH. Aortobronchial fistula after unilateral lung transplantation. *Ann Thorac Surg*. 1993;56(6):1402-1403.
60. Rea F, Marulli G, Loy M, et al. Salvage right pneumonectomy in a patient with bronchial-pulmonary artery fistula after bilateral sequential lung transplantation. *J Heart Lung Transplant*. 2006;25(11):1383-1386.
61. Guth S, Mayer E, Fischer B, Lill J, Weiler N, Oelert H. Bilobectomy for massive hemoptysis after bilateral lung transplantation. *J Thorac Cardiovasc Surg*. 2001;121(6):1194-1195.
62. Kshettry VR, Kroshus TJ, Hertz MI, Hunter DW, Shumway SJ, Bolman RM III. Early and late airway complications after lung

transplantation: incidence and management. *Ann Thorac Surg*. 1997;63(6):1576-1583.

63. Kirk AJ, Conacher ID, Corris PA, Ashcroft T, Dark JH. Successful surgical management of bronchial dehiscence after single-lung transplantation. *Ann Thorac Surg*. 1990;49(1):147-149.
64. Tong MZ, Johnston DR, Pettersson GB. Bronchial artery revascularization in lung transplantation: revival of an abandoned operation. *Curr Opin Organ Transplant*. 2014;19(5):460-467.
65. Alvarez A, Algar J, Santos F, et al. Airway complications after lung transplantation: a review of 151 anastomoses. *Eur J Cardiothorac Surg*. 2001;19(4):381-387.
66. Tong MZ, Johnston DR, Pettersson GB. The role of bronchial artery revascularization in lung transplantation. *Thorac Surg Clin*. 2015;25(1):77-85.
67. Mughal MM, Gildea TR, Murthy S, Pettersson G, DeCamp M, Mehta AC. Short-term deployment of self-expanding metallic stents facilitates healing of bronchial dehiscence. *Am J Respir Crit Care Med*. 2005;172(6):768-771.
68. Cho EN, Haam SJ, Kim SY, Chang YS, Paik HC. Anastomotic airway complications after lung transplantation. *Yonsei Med J*. 2015;56(5):1372-1378.
69. Groetzner J, Kur F, Spelsberg F, et al. Airway anastomosis complications in de novo lung transplantation with sirolimus-based immunosuppression. *J Heart Lung Transplant*. 2004;23(5):632-638.
70. Semenkovich JW, Glazer HS, Anderson DC, Arcidi JM Jr, Cooper JD, Patterson GA. Bronchial dehiscence in lung transplantation: CT evaluation. *Radiology*. 1995;194(1):205-208.
71. Maloney JD, Weigel TL, Love RB. Endoscopic repair of bronchial dehiscence after lung transplantation. *Ann Thorac Surg*. 2001;72(6):2109-2111.
72. Tor M, Musani AI, Gillespie C, Leh S, Kotloff R, Sterman DH. Short-term placement of multiple self-expandable metallic stents for the treatment of bilateral bronchial dehiscences complicating lung transplantation. *J Bronchol Interv Pulmonol*. 2009;16(1):63-65.
73. Nunley DR, Gal AA, Vega JD, Perlino C, Smith P, Lawrence EC. Saprophytic fungal infections and complications involving the bronchial anastomosis following human lung transplantation. *Chest*. 2002;122(4):1185-1191.
74. Sole A, Salavert M. Fungal infections after lung transplantation. *Transplant Rev*. 2008;22(2):89-104.