Review Article



# Lung transplant anastomotic airway complications and bronchoscopic management

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**Abstract:** Airway complications after lung transplantation have significantly reduced in incidence over the past several decades, yet remain a persistent source of morbidity and mortality in this patient population. Complications are most commonly seen at the surgical anastomosis and include regional ischemic necrosis, dehiscence, hypertrophic granulation tissue, fistula, tracheobronchomalacia and bronchial stenosis. The mechanism for developing airway complications is incompletely understood, but may be related to airway ischemia, inflammation or infection that contribute to poor anastomotic and wound healing. Risk factors have been linked to donor and recipient characteristics, perioperative conditions, and immunosuppressive regimens. Flexible bronchoscopy remains the gold standard modality for diagnosis, with airway complications arising in the early and late posttransplant period. The management approach is multifaceted and individualized for each airway complication. Bronchoscopic techniques include balloon or rigid dilation, ablative modalities such as cryotherapy and electrocautery, and in advanced cases, airway stenting. Like other benign airway pathologies, silicone stents are generally preferred to self-expanding metallic stents. Surgery is usually reserved for cases that fail to improve with more conservative measures. Herein, we provide a comprehensive review of the risk factors, clinical manifestations, diagnostic classifications, and management strategies of lung transplant airway complications.

**Keywords:** Lung transplantation; airway complications; anastomotic complications

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## Introduction

Airway complications in the lung transplant recipient have been recognized since the first successful transplantation by Dr. James Hardy in 1963. Airway complications are a continual source of morbidity and mortality in this population with early incidence ranging from 60% to 80%. As the field grew and techniques surrounding transplantation improved, the incidence of airway complications reduced to approximately 2% to 18% (1-5).

Airway complications are known to arise in the early and late posttransplant period with the majority occurring in the first year of transplantation. Complications are varied in their presentation, location, and occurrence, and include regional ischemic necrosis, dehiscence, hypertrophic granulation tissue, fistula, tracheobronchomalacia and bronchial stenosis. The anastomosis is most susceptible to complications, with up to a third of patients experiencing a second airway complication within 2 years of their first (3).

Herein, we provide a comprehensive review of the risk factors, clinical manifestations, diagnostic classifications, and management strategies of lung transplant airway complications.

## Anatomical considerations

Lung anatomy plays a central role in understanding the etiology of airway complications. The lung has a dual blood supply from the bronchial and pulmonary arteries, but the bronchial circulation is not routinely included during lung transplantation. Bronchial arteries arise from the descending thoracic aorta or the intercostal arteries and ultimately terminate in the submucosal plexus of the bronchial wall (6). The proximal mainstem bronchi are primarily supplied by the bronchial circulation, although a small contribution is derived from the pulmonary arterial system through retrograde collaterals. Consequently, the transplanted lung is wholly dependent on retrograde flow via the low pressure, poorly oxygenated pulmonary arterial circulation for bronchial and anastomotic healing. This process continues for 2 to 4 weeks posttransplant placing the anastomosis and distal airways at risk for ischemic injury until revascularization of the bronchial arteries occurs (7,8).

Reestablishing the bronchial circulation at the time of transplantation has been performed successfully using a technique called bronchial artery revascularization (BAR). The experience of two large transplant centers performing BAR was described in a series of 131 patients at Copenhagen and the Cleveland Clinic. The procedure had an overall success rate of 90% with normal airway healing observed in all patients undergoing BAR. The risk of bleeding is higher with BAR, but safety outcomes were similar between BAR and non-BAR groups (9). While these results are promising, BAR is not routinely performed across transplant centers, supporting the need for multicenter studies to establish the safety and efficacy of this procedure in preventing airway complications.

## Risk factors

Multiple risk factors have been linked to airway complications after lung transplantation. A review of the most common risk factors including perioperative, donor and recipient and immunosuppressive medications is provided below.

### *Perioperative factors*

The surgical technique employed in lung transplantation has long been known to influence the development of airway complications. Over the past several decades, the surgical approach to lung transplantation has markedly evolved from the original description of a tracheal anastomosis to that of an end-to-end bronchial anastomosis. The modern-day technique at most institutions is the creation of a direct end-to-end anastomosis as close to the secondary carina as possible. By minimizing the length of the donor bronchus, the anastomotic blood supply is better preserved, and wound healing is more effective (10). Additive techniques such as wrapping the anastomosis with a vascularized pedicle or omental flap may increase the time and difficulty of the procedure without reducing the incidence of airway complications (11). Telescoped anastomoses may be necessary in the event of a donor-recipient size mismatch, but in general should be avoided due to an increased risk for airway obstruction. The telescoped airway is significantly narrowed and may be secondarily compromised by infection with at least one group reporting airway complication rates as high as 32% using this technique (12).

Organ handling and preservation are additional techniques that influence graft perfusion and mucosal healing (13). Preservation solutions that combine low-potassium dextran with glucose and utilization of antegrade plus retrograde administration techniques have been shown to lengthen preservation times and reduce the risk of airway ischemia (14-17). Although donor ischemic time intuitively should impact postoperative airway complications, no study to date has found a direct correlation between the two (3). In fact, for patients undergoing bilateral lung transplantation, the second anastomosis is no more likely to develop an airway complication (18-20). Postoperatively, patients are at risk for primary graft dysfunction, a severe form of ischemia-reperfusion acute lung injury resulting in diffuse alveolar damage, increased vascular permeability and airway ischemia. These patients often require extended periods of mechanical ventilatory support and higher levels of positive end expiratory pressure (PEEP). Greater PEEP values can disrupt bronchial mucosal blood flow, impairing anastomotic healing. Early rejection episodes (within the first 3 months) have also been linked to airway complications due to perturbations in the bronchial microcirculation from increased pulmonary vascular resistance and reduced collateral pulmonary blood flow (13,21).

Infection and microbial colonization pre- and post-operatively can also significantly increase the risk for airway complications. Multiple bacterial and fungal organisms have been implicated (4,21). Aspergillus species, for example, have been shown to increase the risk for airway necrosis (22). As such, clinicians should have a low threshold for investigating and aggressively treating infections in the

 

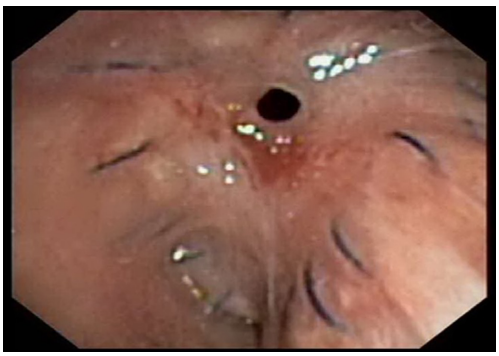

**Figure 1** Airway necrosis.

perioperative period.

### *Donor and recipient factors*

Awori Hayanga and colleagues, in a large retrospective study using shared data from the United Network for Organ Sharing, identified male gender, advancing recipient age and pretransplant admission to the ICU as risk factors for airway complications (23). Van De Wauwer *et al.* in Belgium, also found that taller recipients and prolonged exposure (between 50 and 70 hours) of the donor to mechanical ventilation prior to organ procurement significantly increased the risk for airway complications (24). Factors such as body mass index, organ donor type (brain-dead versus donors after cardiac death), cytomegalovirus status, transplant indication and preoperative corticosteroid use have not demonstrated a consistent impact on the incidence of airway complications (13,21,22,25-28).

### *Immunosuppression*

Immunosuppressant medications are of paramount importance to the survival of the lung allograft. The typical regimen includes a combination of a calcineurin inhibitor, an anti-metabolite, and corticosteroids. These medications increase susceptibility for infection, which if left untreated can increase the risk for airway complications. It has long been debated that steroid impair healing of the anastomosis (29); however, recent studies have shown that steroids in the perioperative period do not compromise airway healing (22,29,30).

Sirolimus has also been used in posttransplant immunosuppressive regimens. It acts by inhibiting the mammalian target of rapamycin and has powerful immunosuppressive and antiproliferative properties. Studies found that sirolimus use in the early posttransplant period was associated with an increased incidence of airway complications, which in some cases were fatal. Therefore, it is recommended that sirolimus be avoided for at least 90 days posttransplant pending complete airway healing (31,32).

## Classification of airway complications

Multiple grading systems have been used to classify airway complications, but no single method has been widely adopted across transplant centers. An early grading schematic proposed by Couraud *et al.* assessed the anastomosis for ischemia and necrosis fifteen days posttransplant. The authors then used this information to subsequently predict anastomotic complications (33). The major limitations of this system included the subjective grading and the inability to capture the full spectrum of airway complications. Shennib and Massard later proposed a classification system that built on the work of Couraud, but included strictures and bronchomalacia in their evaluation (34).

Chhajed *et al.* many years later expanded the grading system for airway complications to include an assessment of the sutures and presence of granulation tissue. This system also described complications at or distal to the anastomosis including bronchial stenosis, malacia and dehiscence (35). Dutau *et al.* in 2013 published the macroscopic, diameter, suture (MDS) grading system, which described the airway abnormality and rated the severity of the complication (36).

A recently published ISHLT consensus statement proposes a universal grading system for adoption across lung transplant centers. This system has four pathophysiologic categories: (I) ischemia and necrosis, (II) dehiscence, (III) stenosis and (IV) malacia. Each category is then further subdivided into the location and extent or severity of the airway complication. The grading system should be applied at regular time intervals within 2–3 weeks of lung transplantation (37).

### *Airway necrosis and dehiscence*

Varying degrees of airway ischemia and necrosis are common during the first few weeks post transplantation (*Figure 1*). These findings are thought to reflect the normal airway healing process during which the necrotic mucosa sloughs and healthy vascularized tissue emerges. Airway dehiscence is a rare, but feared complication with high morbidity and mortality that typically arises during the first 1–6 weeks posttransplant. Dehiscence presumably exists on

 

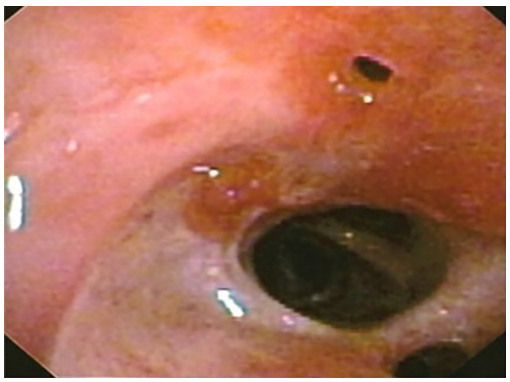

**Figure 2** Dehiscence.

a continuum of ischemic injury and necrosis, and may occur despite an uneventful surgery and postoperative course (38). Prolonged exposure to mechanical ventilation and fungal colonization are proposed risk factors for dehiscence (39).

Diagnosing an airway dehiscence is challenging as the clinical presentation often mimics other complications arising during the early posttransplant period. Red flags that should alert the clinician to a possible dehiscence include a persistent pneumothorax or pneumomediastinum, difficulty weaning from mechanical ventilation and sepsis of unclear origin. Chest computed tomography (CT) is a highly sensitive and specific technique for identifying a dehiscence. CT findings include bronchial wall defects, luminal narrowing and peribronchial air around the anastomosis (40). Flexible bronchoscopy, however, remains the gold standard modality for diagnosis of anastomotic dehiscence (*Figure 2*). Bronchoscopic inspection of the anastomosis as part of a surveillance protocol or for clinical reasons may provide clues to an airway that could undergo dehiscence. Severe necrosis and loosening of sutures are findings that may suggest an anastomosis is at-risk of dehiscing (1,39).

Management of necrosis and dehiscence depends on the location and severity of the defect. If necrotic mucosal slough is observed without evidence of bronchial wall necrosis, then a conservative approach can be taken, including debulking of necrotic debris, aggressive treatment of infection and frequent follow-up bronchoscopies. More severe bronchial wall necrosis and frank dehiscence often require endoscopic or surgical intervention (2,41). Success with bronchoscopic topical therapies such as alpha-cyanoacrylate glue for dehiscence closure is limited to case reports (42). A more common approach involves using an oversized uncovered self-expanding metallic stent (SEMS) to overlap the defect. This technique takes advantage of the SEMS tendency to form granulation tissue at the stent site, which in this case, stimulates healing of the dehiscence. The stent is typically removed after a few weeks as epithelization occurs. If the defect is still present then another oversized uncovered stent can be placed until the dehiscence is sealed. Silicone stents should be avoided as they fail to promote epithelization, and the force required for their insertion risks extending the defect (43). If conservative measures fail then surgery may be considered, including reanastomosis and possibly retransplantation.

Close monitoring after successfully managing the dehiscence is critical as these patients remain at risk for future complications including bronchial stenosis and malacia.

### *Granulation tissue*

Hypertrophic granulation tissue is thought to reflect a robust inflammatory response to airway injury leading to an overgrowth of tissue, similar to a keloidal scar. The reaction typically occurs at the anastomosis within the first several months posttransplant. Signs and symptoms are related to endoluminal obstruction including cough, dyspnea and difficulty clearing secretions. A drop in peak expiratory flows may be seen during spirometry. Like other airway complications, suspicion for this abnormality should be confirmed bronchoscopically (44).

Several techniques can be used to manage excessive granulation tissue in the airway. Mechanical debulking using flexible or rigid forceps is one option, especially for minor obstructions. The beveled edge of the rigid bronchoscope can also be used to core out the tissue, but requires additional skills. Cryotherapy is the preferred modality at our institution since granulation tissue is very cryosensitive. This technique has the additive effect of providing excellent hemostasis during tissue ablation. The safety profile of cryotherapy is superior to that of heat-based modalities, which carry an increased risk for airway fires, bronchial perforation, and gas emboli. Conversely, cryotherapy can be used safely in areas of high oxygen concentration including around stents without risk of ignition (2,45). Mitomycin-C applied topically using pledgets is an adjunctive technique that may prevent recurrence of granulation tissue through inhibition of fibroblast proliferation (46).

### *Fistula*

Fistula formation is an uncommon complication in the lung

 

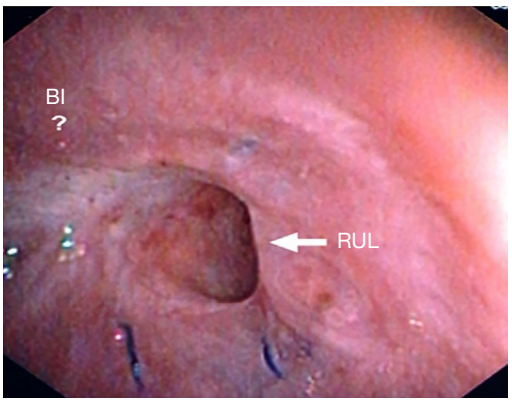


**Figure 3** Bronchomalacia. BI, bronchus intermedius; RUL, right upper lobe.

transplant population. Fistulous connections may occur between the airway wall and the pleura, vascular space, or mediastinum. Clinical findings of a bronchopleural fistula include shortness of breath, subcutaneous emphysema, and pneumothorax with a persistent air leak. Closure of the fistula can be accomplished surgically or bronchoscopically. The preferred approach is akin to management of a dehiscence using an uncovered stent to seal the defect (2).

A bronchovascular fistula is a rare and often fatal complication. The typical location of the defect is between the anastomosis and the pulmonary artery. A sentinel bleed may precede the development of massive hemoptysis. Management options are limited to endovascular stenting, fistula repair and transplant pneumonectomy (47-49).

### *Tracheobronchomalacia (TBM)*

TBM is a condition characterized by softening of the supportive cartilage of the tracheal and bronchial wall and reduced tone of myoelastic elements. This results in cartilage weakening and endoluminal narrowing of at least 50% during forced expiration. The incidence of airway malacia in the posttransplant population is unknown. Recurrent infection and ischemic injury are suspected predisposing factors, or in some cases, the condition may have been missed in the donor lung prior to transplant. The malacic segment may be at the level of, distal or proximal to the anastomosis (50,51).

Clinical manifestations of TBM are often indistinguishable from other chronic lung pathologies. Dyspnea, cough, and inability to clear secretions are the most commonly reported symptoms. A characteristic, seal-like barking cough may arise during expiratory collapse of the posterior membrane reverberating against the anterior wall. Additional patient complaints may include wheezing, stridor and recurrent infections.

Diagnostic studies routinely employed for TBM include dynamic CT imaging and bronchoscopy. Paired inspiratory-dynamic expiratory CT imaging involves scanning the patient at end inspiration and during forced expiration. The change in cross-sectional area and sagittal diameters of the airway between inspiration and expiration may reliably predict the presence of TBM (52). Dynamic flexible bronchoscopy, however, remains the gold standard modality for diagnosing this condition (*Figure 3*). This procedure enables real-time visualization of the airway dynamics, degree of collapse, cartilage integrity and classification of the type and extent of TBM. During dynamic bronchoscopy, the patient is lightly sedated, and instructed to perform various maneuvers, including deep inhalation, cough, and forceful exhalation. The exam is repeated at different locations in the tracheobronchial tree to assess the extent of airway malacia. Operators are then able to calculate the airway cross-sectional area, although inter- and intra-observer disagreement exists (50,53).

Management of posttransplant TBM follows the same therapeutic principles applied to the non-transplant population. Airway irritants such as smoke and gastric acid should be eliminated or optimally controlled. Continuous positive airway pressure (CPAP) is a commonly used non-invasive modality that reduces airway resistance, improves expiratory flow, and facilitates secretion drainage by creating a pneumatic splint. Airway stents can restore endoluminal patency and provide symptomatic relief, but generally are used as part of a short-term therapeutic trial to assess a patient's response to central airway stabilization. If a stent trial is successful then patients can be considered for surgery. Tracheobronchoplasty is a surgical option for patients with TBM that involves splinting the posterior membranous wall using a polypropylene mesh, preventing endoluminal invagination. Referral to a center with expertise in this operation is strongly recommended (54,55).

### *Bronchial stenosis*

Bronchial stenosis is the most common airway complication after lung transplantation, with incidence rates ranging from 1.6% to 32% (12,56-58). The etiology of bronchial stenosis is likely multifactorial with inflammation, ischemia and infection cited as potential contributing factors (59).

 

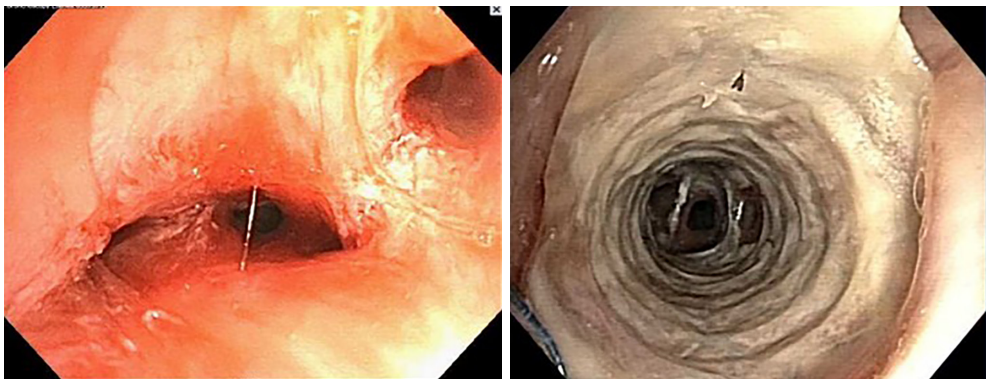

**Figure 4** Central anastomotic stenosis.

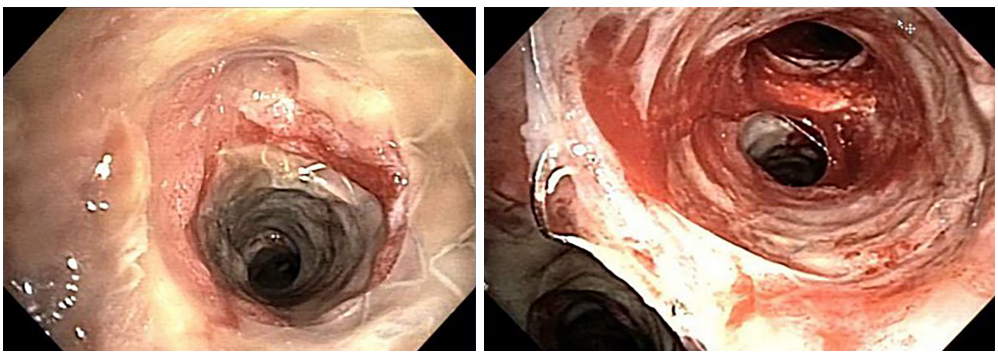

**Figure 5** Distal lobar stenosis.

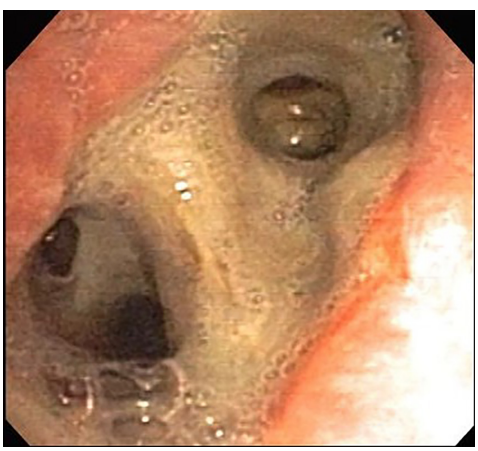

**Figure 6** Complete stenosis of the bronchus intermedius.

The site of stenosis is often divided into two types: central and distal. Central airway stenosis is located at or within 2 cm of the anastomotic suture line (*Figure 4*). Distal or non-anastomotic stenosis involves the lobar, segmental and subsegmental airways (1,37,60) (*Figure 5*). The most common non-anastomotic site of stenosis is the bronchus intermedius, which may result in complete stenosis or vanishing bronchus intermedius syndrome (VBIS) (*Figure 6*). VBIS is technically very difficult to manage conferring a mean survival of 25 months from the time of diagnosis (61,62).

Signs and symptoms of bronchial stenosis are usually non-specific. In many instances, the diagnosis is uncovered during routine imaging or surveillance bronchoscopy. Dyspnea, cough, wheezing and inability to clear secretions are the most common patient complaints. Spirometric findings may include diminution of peak expiratory flow and flattening of the flow-volume loop (63). Chest imaging can also be a useful adjunct for the diagnosis of bronchial stenosis. For example, a focal stricture or narrowing may be seen, or in the case of VBIS, complete collapse of the right middle and lower lobe. However, like other airway complications, bronchoscopy remains the gold standard modality for diagnosis (2,34,62).

The management of bronchial stenosis is often

 

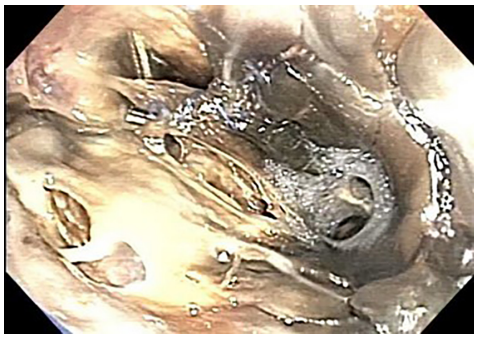

**Figure 7** Stenosis of right bronchus intermedius, right middle lobe & right lower lobe with iCast stent placement.

individualized and dependent on local expertise and available treatment options. An objective assessment of symptom burden (i.e., using dyspnea scores or pulmonary function testing) should be sought prior to and immediately after any intervention to document response. Therapeutic maneuvers that may be combined or used in isolation include endobronchial dilation, ablative modalities, and stenting. Balloon dilation is a common initial technique that may achieve durable results when performed alone. However, repeated dilations at regular intervals may be required to provide sustained symptomatic relief (35,64). Airway dilation can be achieved using an inflatable balloon or rigid bronchoscopy. While neither of these techniques has been shown superior to the other, the balloon has several distinct advantages. The balloon is translucent allowing the operator to visualize the airway during dilation, and then select the inflation pressure needed to optimally dilate while avoiding mucosal tearing. Inflatable balloons are also available in different sizes and lengths that fit through the working channel of a flexible bronchoscope. The ability to select and alternate between balloons is a faster and simpler option when compared to serially upsizing with a rigid bronchoscope for dilation. A noteworthy point with the balloon occlusion technique is ventilation will be interrupted. In contrast, the rigid bronchoscope has the advantage of providing collateral ventilation through its side ports. Additionally, if silicone stenting or debulking is anticipated during the same procedure then the rigid scope may be preferred (2,65).

Multiple ablative techniques can be used to treat bronchial stenosis including laser, cryotherapy, argon plasma coagulation and photodynamic therapy. The preferred modality at our institution is the electrocautery blade, which is used to make small incisions in the stenotic scar. Using this technique, the scar will preferentially tear in the previously incised areas during airway dilation. Mitomycin-C is sometimes applied topically after the procedure to prevent scar tissue formation.

Airway stenting is an option typically reserved for recurrent stenosis. Stenting in the transplant population must be carefully considered because of their immunocompromised status and higher risk for complications. If indicated and performed correctly, stenting can achieve excellent results. Silicone stents are preferred to SEMS for any benign stenosis, including those arising in the lung transplant recipient. Unlike SEMS, silicone stents can only be inserted through a rigid bronchoscope. The advantage of silicone when compared to SEMS is a lower incidence of granulation tissue formation, which makes removal easier, even if the stent has been present for a long time. Silicone can also be modified to a desired length and notched to prevent blockage of an airway orifice. Drawbacks of silicone stents include a higher risk for migration, mucous plugging, and halitosis. SEMS on the other hand offer the advantage of being deployable through a flexible bronchoscope. In addition, the internal to external diameter of the SEMS is more favorable and migration is less common. A challenging scenario arises when SEMS are left in place for extended periods and granulation tissue forms, making removal technically challenging. Additional complications include stent fracture, bacterial colonization, and restenosis (65-67) (*Figure* 7). The airway stents mentioned above are traditionally used in central airways to maintain patency, however many lung transplant patients have lobar and segmental bronchial stenosis. Recently, we published a case series at the Cleveland Clinic utilizing a polytetrafluoroethylene covered stainless steel balloon deployed stent (Atrium iCast stent) in lung transplant patients with lobar bronchial stenosis with exceptionally good outcomes (68) (*Figure 8*). These stents were found to be safe and improved symptoms as well as radiographic outcomes.

## Conclusions

Despite advances in the field, airway complications after lung transplantation remain a consistent source of morbidity and mortality in this patient population. The management varies depending on the type of complication with no studies showing that one treatment modality is superior to another, underscoring the need to discuss these cases in a multidisciplinary setting. Further investigation is

 

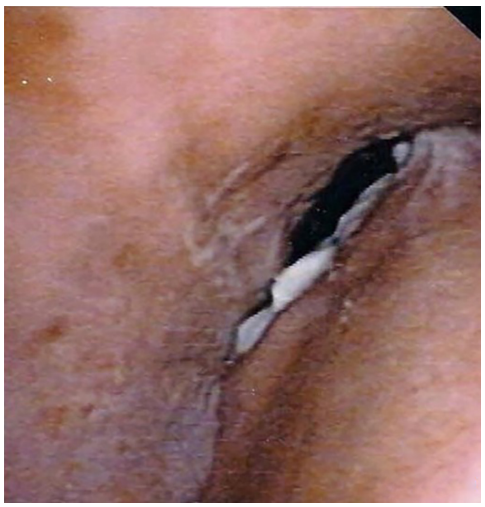

**Figure 8** Left upper lobe stenosis with iCast stent placement.

needed to define the optimal treatment algorithm for each of these complications. Referral to a center with expertise in managing airway complications is strongly recommended.

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