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ISHLT Consensus Statement on adult and pediatric airway complications after lung transplantation: Definitions, grading system, and therapeutics

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Airway complications remain a major cause of morbidity and mortality after cardiothoracic transplantation. The reported incidence of airway ischemic complications varies widely, contributed to by the lack of a universally accepted grading system and standardized definitions. Furthermore, the majority of the existing classification systems fail to integrate the wide range of possible bronchial complications that may develop after lung transplant. Hence, a Working Group was created by the International Society for Heart and Lung Transplantation with the aim of elaborating a universal definition of adult and pediatric airway complications and grading system. One such area of focus is to understand the problem in the context of a more standardized consensus of classifying

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airway ischemia. This consensus definition will have major clinical, therapeutics, and research implications.
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After Professor James Hardy performed the first human lung transplant in 1963, airway complications were found to be a significant source of morbidity and mortality.[1] In 1970, a review of 23 lung transplants performed by 20 surgeons identified 13 patients with bronchial anastomotic complications and only 1 long-term survivor.[2] Revisions of the anastomotic technique, advances in organ preservation, improved donor–recipient matching, and medical management have led to a marked reduction in acute airway injury. Nevertheless, large contemporary studies continue to report airway complication rates, ranging from 2% to 18%.[3–6] This variation is due in part to inconsistent definitions and follow-up protocols, but also suggests an opportunity to reduce overall complications through improved identification and the application of optimal techniques and management strategies. Post–lung transplant airway complications may occur early or late after surgery, involve the anastomosis or distal airways, include varying degrees of ischemia and necrosis, or evolve to dehiscence, stricture formation, and bronchomalacia. A standardized reporting system is necessary to accurately determine the prevalence, impact, and management strategy for each type of airway complication.

Several classification systems have been proposed, but none have been accepted as a "gold standard" by the transplant community. An early publication by Couraud et al, in 1992, described the macroscopic appearance of the bronchial anastomosis assessed at Day 15 after lung transplantation.[7] This system describes anastomotic ischemia and necrosis, but it does not apply to the distal airway and does not incorporate the full spectrum of pathology. Shennib and Massard presented a more expansive classification in 1994, describing a spectrum of airway complications from early ischemic change to fibrotic strictures and bronchomalacia.[8] This system included a comprehensive assessment of ischemia and necrosis, but it is limited in its treatment of stenosis and is not designed to describe simultaneous pathologies. The TEGLA classification for bronchoscopic reporting of airway ischemic injury was proposed by Chhajed et al in 2004.[9] This classification describes the thickness of mucosal injury (T), extent of circumferential injury (E), the existence of granulation tissue (G), the appearance of loose sutures (L), and the presence of anastomotic or distal airway complications (A). The TEGLA system does not include standardized grading metrics for all complications. Dehiscence and stenosis are dichotomous variables, with severity and location entered as free text. Thistlethwaite et al proposed a stenosis grading system in 2008 that recognized differential location, but it does not incorporate measures of severity and does not include other complications.[10] The classification system described by Santacruz and Mehta in 2009 outlines 6 categories of airway complications, and includes many of the insights from earlier systems.[11] However, this system does not separate dehiscence from necrosis and is not constructed as a grading system *per se*. Finally, the macroscopic, diameter, suture (MDS) grading system was published in 2013 by the French Language Pulmonary Society.[12] This classification system uses a tiered approach to document descriptive endoscopic features of airway complications. Although the MDS scheme is the most comprehensive grading system to date, it does not rate severity of ischemia and necrosis, which is particularly important in evaluating the early post-transplant airway, thus making it difficult to link these early findings with long-term complications identified in longitudinal follow-up.

The ideal grading system should build on the strengths of these existing classification methods. It should encompass the spectrum of early and late airway complications and each complication must be described objectively in terms of severity, propagation, and location. It must be reproducible, well-defined, and clinically relevant. The system must facilitate comparison between different observers and across different points in time, enabling multi-institutional research so we may understand this important source of post-transplant morbidity.

Pathophysiology

The etiology of airway complications after lung transplantation has been attributed mostly to donor bronchial ischemia.[13–16] Bronchial blood supply is normally derived from the pulmonary and bronchial arteries, which collateralize in the sub-mucosal plexus.[16,17] Bronchial arteries arise from the descending aorta or intercostal arteries and track through the pulmonary hilum adjacent to the bronchus. Small arteriolar branches penetrate the muscular portion of the bronchial wall to form a sub-mucosal plexus with small divisions of the pulmonary arterial bed. The bronchial arteries are typically transected at the time of lung procurement. Allograft airways are therefore acutely dependent on retrograde flow from the low-pressure, poorly oxygenated pulmonary arterial system. Revascularization of the donor airway by the recipient bronchial circulation typically occurs over 2 to 4 weeks.[8,13] In contrast, the tracheal anastomosis of heart–lung transplantation has an excellent proximal airway blood supply from atrial branches of the donor left and right coronary circulation, collateralizing with the bronchial arteries.[11]

Until neo-vascularization occurs, factors that decrease pulmonary blood flow or increase pulmonary vascular

resistance worsen donor bronchial ischemia. These factors include poor graft preservation, lung ischemia–reperfusion injury, severe edema, rejection, infection, inflammation, and prolonged positive pressure ventilation.[10–26] Likewise, an excessive length of donor bronchus exacerbates ischemia at the level of the anastomosis.[8,14–19]

Donor airway ischemia presents initially with mucosal changes. Progressive ischemia may lead to necrosis of the bronchial wall and, eventually, dehiscence. Early ischemic changes are thought to contribute to fibrosis, granulation tissue formation, and compromised structural integrity of the airway.[20–22] These processes have long-term consequences evident clinically as stenosis and malacia.

Risk factors

Multiple risk factors have been associated with airway complications. Compromised blood flow is the suspected final common pathway for many but not all of these risk factors.[15,20]

Donor and recipient characteristics

Both length of donor's mechanical ventilation support time (>50 to 70 hours) before organ recovery and donor and recipient height mismatch have been identified as risk factors for airway complications.[19,20] It is hypothesized that this mismatch results in a difference in bronchial circumference due to the direct relationship between height and bronchial circumference.[8,14,19] To avoid these risk factors, careful assessment of donor clinical status as well as matching donor and recipient height is of utmost importance. No difference in incidence of airway ischemia has been reported using donation after circulatory determination of death (DCDD) donors, as opposed to donation after neurologic determination of death (DNDD) donors.[27,28]

Hypoperfusion

It is hypothesized that prolonged hypoperfusion due to pathophysiologic (hypotension or low cardiac output) or iatrogenic factors may increase the risk of airway complications in patients undergoing lung transplantation. Reduced perfusion may lead to ischemia, especially in structures undergoing surgical manipulation such as an anastomosed airway. This notion was supported by early studies demonstrating that over half of the patients with airway complications had severe post-operative hypotension.[29]

Right-sided anastomoses

Right-sided airway anastomoses are more than twice as likely to develop airway complications after lung transplantation as left-sided anastomoses.[4] Bronchi normally receive circulation from both the pulmonary and bronchial arteries, which collateralize in the sub-mucosal plexus.[16,17] However, variability of the vascularization exists between the right and left bronchi. Compared with the left bronchus, which is perfused by 2 bronchial arteries, the right bronchus is only perfused by 1 bronchial artery. In addition, the right bronchial artery can arise from several locations, including the thoracic aorta, the left superior bronchial artery, and right intercostal arteries. Although the left bronchial artery arises directly from the anterior surface of the thoracic aorta, the anteromedial surface of the aortic arch, lateral to the carina, and posterior to the left main bronchus.

Organ preservation

Organ procurement techniques may also have implications with regard to airway ischemia and complications. Bronchial healing may be compromised if the airways are improperly manipulated or preserved before implantation. Resulting endothelial edema and reperfusion injury decrease retrograde bronchial perfusion, leading to increased risk of ischemia.[20] The choice of perfusate has been shown to greatly decrease this risk.[30–34] In canine models, the use of low-potassium dextran preservation solutions led to successful 12-hour lung preservation times, and the addition of glucose to this solution extended this time to 24 hours.[30] Because of these findings, Perfadex was formulated (a low-potassium dextran + glucose solution) to help avoid this deleterious pathway during the procurement and preservation stages of lung transplantation.[32]

The technique of administering the preservation solution is also important in decreasing the incidence of airway ischemia post–lung transplant. Several studies have shown superior results in utilizing antegrade and retrograde administration of preservation solutions compared with organs that were perfused with antegrade administration alone.[33,34] The addition of prostaglandin E_1 has been shown to safely extend preservation times to 22 to 24 hours and improves the distribution of perfusate through pulmonary vasodilation.[34]

Mechanical ventilation

Although mechanical ventilation is necessary in the perioperative management of both donor and recipient, there is evidence that both the duration and technique of ventilator support may contribute to airway ischemia. In one study, donor mechanical ventilation between 50 and 70 hours was found to be a risk factor for airway complications after lung transplantation.[19] Post-operative mechanical ventilation, and higher levels of positive end-expiratory pressure (PEEP) in particular, may disrupt airway mucosal and anastomotic suture-line healing.[6,11,21,22,24–26] When using laser Doppler velocimetry in canine lung transplant models, PEEP has been demonstrated to negatively affect bronchial mucosal blood flow.[23] As such, special attention is necessary whenever increasing PEEP in lung transplant recipients due to the delicate state of each anastomosis.

Primary graft dysfunction

Patients undergoing primary graft dysfunction (PGD), a form of acute lung injury related to ischemia–reperfusion,

are also at increased risk of airway ischemia. These patients develop alveolar damage and increased vascular permeability. Airway ischemia may result from PGD due to the development of interstitial edema and reduction of pulmonary flow.[14,22,46–48] Moreover, patients with severe PGD require longer mechanical ventilation as well as the degree of PEEP required, which have been shown to contribute to bronchial wall and anastomotic stress.[6,11,22]

Microbiologic contamination

Microbiologic contamination can greatly impact the healing of airway anastomoses.[6,14,18,35] Despite systemic and nebulized prophylactic anti-microbial agents, several organisms, specifically fungi, have been associated with the development of airway complications, including *Aspergillus*, *Candida*, *Rhizopus*, and *Mucor* species.[6,18,35] Before transplantation, anastomoses are constructed using sterile techniques, however the incidence of airway colonization still exits which may lead to airway complications.[6,14,18,19,35] It is hypothesized that local ischemia may compromise the integrity of the mucosal barrier, thus allowing colonized organisms to invade the bronchial wall and cause a localized infection, which then further promotes ischemia and necrosis. Management of pre-operative airway colonization and the meticulous treatment of early post-operative bronchial infections may help to reduce the incidence of airway complications.[4,14,18,19,35] However, the actual role of infection leading to airway complications is not firmly established.

Immunosuppression

Mammalian target-of-rapamycin (mTOR) inhibitors, such as sirolimus, have been shown to disrupt airway healing and dramatically increase the rate of catastrophic airway complications in de novo lung transplant recipients. In particular, the rate of dehiscence was found to be unacceptably high in the early transplant period.[36,37] The current recommendation is avoidance of mTOR inhibitors until healing of the anastomosis is confirmed bronchoscopically.[36,37]

The use of corticosteroids in the pre-operative period was once considered a contraindication because of concern for anastomotic healing.[38] However, later studies showed no adverse effect, less granulation tissue formation, and improved survival in the face of corticosteroids.[8,18,21,38–40] Most authors now agree that steroids are not detrimental to the healing of the anastomosis and the withholding of corticosteroids is therefore not justified.

Acute cellular rejection

There is controversy regarding the association between acute cellular rejection (ACR) and airway ischemia. In the setting of ACR, reduction in graft perfusion has been documented via laser Doppler measurements of submucosal blood flow.[41] This is due to several physiologic changes that occur during ACR episodes, including sub-mucosal edema caused by acute inflammation as well as increased vascular resistance to collateral flow. Nonetheless, several studies have failed to identify a clear relationship between the incidence of ACR and airway ischemia leading to dehiscence.[6,13,39,42,43] ACR affects overall survival of patients and their grafts and may increase bronchial stricture formation.[13,42] Steroid treatment for ACR should therefore not be delayed for fear of interrupting anastomotic healing, as many studies have shown no increased rate of airway complications or mortality associated with the use of steroids.[8,18,21,39,42,43] The use of bronchial artery revascularization during lung transplantation may be associated with decreased incidence of early ACR (<3 months after transplant), but further studies are needed to fully investigate this finding.[44,45]

Ischemic time

There is also controversy over the association between ischemic time and post-operative airway complications after lung transplantation. Inevitably, prolonged organ ischemic times will result in increased airway ischemia, but it is unclear to what extent preservation techniques are able to mitigate the impact of this effect. Multiple studies have failed to show a direct correlation between length of donor ischemic time and development of post-operative ischemic airway complications.[6,13,39,42] Moreover, there is no increase in the incidence of ischemic airway complications involving the second anastomoses in patients undergoing bilateral lung transplantation.[24–26,29] Although there may not be any implications involved in terms of airway ischemia, excess ischemic times should be avoided due to its association with outcomes.[46–48] The impact of warm ischemic time has not been thoroughly investigated to date.

Surgery

Surgical techniques have an obvious influence on the incidence of complications and such techniques have changed dramatically over the last 30 years. The original technique of tracheal anastomosis for bilateral lung transplantation was associated with profound anastomotic ischemia. The incidence of anastomotic complications was so high that this technique was largely abandoned.[8,24,42,43] Early techniques of sequential double lung transplant involved a planned site of donor bronchial transection 3 or 4 rings proximal to the secondary carina. This excessively long donor bronchus contributed to a high incidence of airway complications.[8,14,16,19] Early transplant techniques routinely employed the use of omental flaps to wrap the anastomoses. This added significantly to the duration and complexity of the operations and did not eliminate anastomotic complications.[8,22,42] Other approaches used intercostal muscle flaps, internal mammary arterial pedicles, and pedicled peri-cardial fat pads. These techniques also failed to have a significant impact in the incidence of airway complications.[49]

More modern techniques involve minimizing the length of donor bronchus as much as possible and preserving blood supply.[8,14,16,19] Although dissection of fat and lymphatic tissue away from the proposed site of anastomosis may enhance exposure, there is evidence to support that this approach may lead to more ischemia.[22,29] All attempts should be made to minimize skeletonization of the donor bronchus to avoid disruption of the microcirculation. This also significantly prolongs the duration of operation, is technically demanding, and has not definitively been shown to reduce airway complications.

To minimize airway ischemia, the technique of bronchial arterial revascularization (BAR) with lung transplantation has been reported.[44,45,50–56] Successful lung transplant with BAR requires: (1) lung donor procurement that includes the proximal descending aorta and preservation of the donor bronchial artery/arteries; (2) accurate identification of the bronchial artery/arteries during back-table donor organ preparation; and (3) primary revascularization of the bronchial artery/arteries with an aortic patch technique or with internal mammary artery or venous conduit.[51–53] A limited number of recent, retrospective, single-center studies reported lower rates of airway ischemia with BAR in both adults and children.[54,55] The role of BAR in mitigating longer term complications, such as bronchiolitis obliterans syndrome, remains controversial.[56,57]

The type of anastomotic reconstructive technique may also influence outcomes. If a size disparity exists between donor and recipient bronchi, telescoping can compensate for the mismatch. The recipient or donor bronchus can serve as intususseptum or intususseptiens, depending on the direction of disparity. However, deliberate telescoping of bronchi of similar size has been shown to increase buckling and the development of airway stenosis.[57] Whenever possible, a direct end-to-end technique is preferred.[58] Running and interrupted suture techniques may also play a role. Running or continuous suture techniques introduce a risk of purse-stringing, particularly if malacia is present and excessive tension is applied to the suture. Interrupted techniques take more time to complete but yield reproducible results.[5,6,9,22,59,60] Figure-of-eight sutures coapt the edges of donor and recipient airways more effectively than simpler techniques.[5] This technique may help limit the formation of pockets or irregularities in the anastomoses that would allow for pooling of secretions and compromise of airway healing. The membranous portion of the anastomoses tends to be less vulnerable than the cartilaginous portion. Although poorly investigated, different techniques may be used safely for the membranous and cartilaginous portions of the reconstruction. There has been no definitive advantage of one anastomotic technique over another in the literature.[13,58]

Mulligan and colleagues presented their results with a hybrid anastomotic technique.[5] Their analysis included 230 patients, representing 407 anastomoses. They compared the results with the new technique to a matched cohort of patients whose anastomoses were constructed with a continuous running polypropylene suture 1 or 2 cartilaginous rings from the secondary carina. With the new technique, the length of the donor bronchus is minimized by resecting the donor mainstem bronchus, creating the anastomosis at the secondary carina. A running suture is placed along the membranous portion of the bronchi, followed by figure-of-eight stitches into the cartilaginous membrane. The figure-of eight sutures are pulled taut at the same time to avoid distortion and allow the natural lie to develop. Intentional telescoping is not performed, but, when there is a size difference, the smaller bronchus is allowed to intussuscept into the larger airway.

This technique resulted in a statistically significant decrease in the number of anastomotic complications requiring intervention after lung transplant. Specifically, there was a decrease from 21.6% to 4.4% by patient or 18.1% to 2.3% by anastomosis, respectively. The authors also found a corresponding decrease in the incidence of distal airway complications, from 12.2% to 4.4% of patients. A similar experience with this technique was reported by Dark and colleagues, whereas other groups subsequently reported their ability to reproduce these results.[3,59] It is noteworthy, however, that the anastomotic technique and its complications have never been tested in a randomized, controlled trial.

One concern with this technique is the limitation of salvage options if airway complications do develop. With severe airway complications, a skilled interventional bronchoscopist is essential for dilatation and complex stent placement. If resective management is necessary, a sleeve resection and re-implantation of the main-stem bronchus cannot be performed given the previous resection of the donor main-stem bronchus. In this setting, a lobectomy, sleeve lobectomy with lobar reimplantation, or retransplantation may be the only options available for management of the disease. Further studies are needed in the modern era to completely define the optimal anastomotic approach.

Classification of airway complications

Ischemia, necrosis, and dehiscence

Dehiscence

The reported incidence of anastomotic dehiscence ranges between 1% and 10%.[11] This may be sub-divided into partial or complete dehiscence and is usually the result of mucosal necrosis as a complication of significant airway ischemia occurring within the first 1 to 6 weeks after transplantation. Airway dehiscence to a lesser degree has been described in up to 24% of cases,[57] with the most severe degrees of airway dehiscence being observed in $<2\%$ of lung transplant recipients.[4,11,68] Dehiscence is associated with very high mortality and surveillance for this complication during routine bronchoscopy is mandatory. In a pediatric study from St. Louis, 37% of lung transplant recipients with airway dehiscence were asymptomatic and problems were found incidentally on surveillance bronchoscopy.[60] The outcome of airway dehiscence varies depending on the severity, with most patients dying from infection and sepsis secondary to the complication.

Chest computed tomography (CT) aids in the detection and evaluation of subtle extraluminal air collections. Chest CT imaging was associated with 100% sensitivity and 94% specificity for the detection of dehiscence proved by bronchoscopy in a cohort of 23 patients after single or bilateral lung transplantation.[61] Peri-bronchial air and bronchial wall irregularities, wall defects, dynamic or fixed bronchial narrowing, and dissection into the mediastinum, or a combination of these, are radiologic manifestations on chest CT of anastomotic dehiscence.[13,61,66] However, others have shown that chest CT findings of a bronchial defect and extraluminal air did not assist in the prediction of interventional requirements when recipients have larger amounts of extraluminal air (>4 mm of dehiscence).[68] Furthermore, mucosal necrosis (the earliest sign and a predictor of airway dehiscence) is not reliably illustrated on chest CT scan. Thus, bronchoscopy is considered the gold standard for confirmation of the diagnosis and guides further management.[63] It is important to note that the role of surveillance bronchoscopy for the detection of airway dehiscence over clinically indicated bronchoscopy has not been determined to date, as there are no prospective, randomized studies examining the utility of surveillance.

Stenosis

Bronchial stenosis is the most common airway complication after lung transplantation. Two types of bronchial stenosis have been described. The first is located at the bronchial anastomosis or within 2 cm of the anastomosis and is classified as central airway stenosis (CAS). The second type affects the airways distal to the anastomosis or the lobar bronchi, called distal airway stenosis (DAS), and can exist with or without CAS. DAS is poorly described in the literature and is often not differentiated from CAS in many cohorts. The incidence of DAS has been noted to range from 2.5% to 3% in the limited literature available,[63,64] but this is likely an underestimation due to poor differentiation in older classifications between DAS or CAS. This lack of differentiation has contributed to poor understanding of the etiology and potential treatment of DAS. DAS most commonly occurs at the bronchus intermedius, leading to complete stenosis or vanishing bronchus intermedius syndrome (VBIS), which is found in about 2% of cases.[64,84] This form of DAS has a significant impact on morbidity and mortality, with a mean survival of 25 months after diagnosis of VBIS.[64,84]

Malacia

Airway malacia is defined as a >50% reduction in luminal caliber with expiration.[88] Malacia results from loss of cartilaginous support within the airways. These changes may occur both at the anastomosis and more diffusely throughout the donor airway. Presenting symptoms include dyspnea, especially with recumbent position, increased work of breathing, difficulty with secretion clearance, recurrent infections, and a chronic cough often with a "barking" character. Spirometry shows reductions in forced expiratory volume in 1 second (FEV_1), and forced expiratory flow both at peak and at 25% to 75% peak.[88] Flow-volume loops may show blunted peak flows and a variable expiratory trace suggesting dynamic obstruction. Dynamic inspiratory–expiratory CT scans may be suggestive of malacia, but bronchoscopy is the gold standard for diagnosis.[66,88]

Methodology

The International Society for Heart and Lung Transplantation (ISHLT) formed a Writing Committee to obtain a consensus among experts on such a grading system, and to facilitate its adoption within the transplant community. The following proposed grading system is based on expert consensus and builds on previous classification schemes. The panel members are recognized leaders in the field of adult and pediatric cardiothoracic transplantation, and were selected from established transplant centers worldwide by the chairs. The panel members approved the most relevant questions to be addressed in the areas of epidemiology, definitions, grading classification, and treatment. The panel was subsequently divided into working groups, each headed by their respective chairs. A comprehensive literature search was performed by the panel chairs and was disseminated to the working groups. The working groups reviewed the existing literature to answer the identified questions based on the published evidence, and to provide guidance based on prevailing expert knowledge and experience. Each group reviewed, evaluated, and summarized the relevant evidence and then presented their findings to the working group by teleconference and at the 2016 ISHLT Meeting in Washington, DC. The recommendations were graded according to the ISHLT Standards and Guidelines Committee documents. Disagreements were resolved by iterative discussion and consensus. Subsequently, each group chair prepared an article with input from the members of the group and submitted it to the co-chairs. These articles were modified based on the feedback of the co-chairs. The executive summaries for each topic were generated from the articles from the co-chairs and were submitted to the ISHLT Standards and Guidelines Committee. Each panel member disclosed his or her conflicts of interest.

Classification: Proposed grading system

The basic unit of analysis is the nature of the pathophysiologic change (i.e., type): ischemia and necrosis; dehiscence; stenosis; or malacia. These terms are defined in Table 1 and are demonstrated in the endoscopic visual atlas in the Supplementary Material (available online at www.jhltonline.org). Each type of complication is then further graded based on what part of the tracheobronchial tree is involved (location), and severity of the pathologic process (extent). This proposed grading system is based on the first bronchoscopy findings within 2 to 3 weeks after lung transplant, and the trajectory of changes may be assessed

Table 1 ISHLT Adult and Pediatric Airway Complications After Lung Transplant: Propose Grading System

Ischemia and Necrosis (I)

Location

a. Perianastomotic—within 1 cm of anastomosis
b. Extending >1 cm from anastomosis to major airways (bronchus intermedius and distal left main-stem)
c. Extending >1 cm from anastomosis into lobar or segmental airways

Extent

a. <50% circumferential ischemia
b. >50% to 100% circumferential ischemia
c. <50% circumferential necrosis
d. >50% to 100% circumferential necrosis

Dehiscence (D)

Location

a. Cartilaginous
b. Membranous
c. Both

Extent

a. 0% to 25% of circumference
b. >25% to 50% of circumference
c. >50% to 75% of circumference
d. >75% of circumference

Stenosis (S)

Location

a. Anastomotic
b. Anastomotic plus lobar/segmental
c. Lobar/segmental only

Extent

a. 0% to 25% reduction in cross-sectional area
b. >25% to 50% reduction in cross-sectional area
c. >50% but <100% reduction in cross-sectional area
d. 100% obstruction

Malacia (M)

Location

a. Perianastomotic—within 1 cm of anastomosis
b. Diffuse—involving anastomosis and extending beyond 1 cm

with repeated procedures. Recommendations for specific time-points (T points) of airway assessment need to be flexible enough to take into account the variation in time to first bronchoscopy inspection and subsequent evaluation of allograft function among transplant centers. Documentation of T points, such as Week 1 (TW1), Week 3 (TW3), and Month 1 (TM1), enables such a universal reporting system to accurately document when the assessments are occurring.

It is very important to recognize other types of airway pathology, like endobronchial fungal infections and endobronchial post-transplant lymphoproliferative disorder (PTLD), which can present as airway necrosis or stricture.

For the purposes of this grading system, the following definitions are proposed based on endoscopic characteristics of the pathology. *Ischemia* is manifested as inflammatory infiltration with mucosal edema, hyperemia, and/or pseudomembrane formation from mucosal sloughing. Judgment must be used to differentiate mild ischemia from infectious changes when there is clinical suspicion for tracheobronchitis. *Necrosis* presents as gray–black devitalized plaque involving deeper layers of the bronchial wall. Because ischemia and necrosis are essentially a continuum of the same process, they are included within the same type but distinguished according to different grades of severity. *Dehiscence* is full-thickness separation of the bronchial wall at the anastomosis. In the early post-operative period dehiscence is typically associated with varying degrees of ischemia and necrosis. However, dehiscence is distinguished as a unique type of airway complication because ischemia and necrosis can occur in the absence of dehiscence, and dehiscence has major implications for management. *Stenosis* is defined as a fixed reduction in caliber of the airway. When stenosis occurs at an anastomosis, it is based on the caliber of the distal airway to differentiate pathologic stenosis from simple size mismatch between donor and recipient airways. The narrowing may be due to various underlying mechanisms (e.g., granulation tissue, fibrosis), but these subtypes are not included in the grading system in an effort to maintain simplicity. When grading the severity of stenosis, complete (100%) obstruction is identified separately based on significant differences in managing this complication. Finally, *malacia* is defined as a dynamic reduction of the airway caliber of >50% during expiration. Because it is difficult to determine precisely the degree of malacia, the grading system does not assess severity of malacia, rather it is treated as a binary variable.

Management

Ischemia, necrosis, and dehiscence

Dehiscence

There is no clear universal consensus on the best therapeutic approach for anastomotic dehiscence, and management practice has been driven by the severity of necrosis and the presence of any associated complications.

If necrosis involves the mucosa but not the bronchial wall and no air leak is detected, then conservative management with antibiotic treatment and surveillance bronchoscopy is usually adequate. Chest drainage will be required in the presence of a pneumothorax and air leak. Patients should undergo frequent follow-up bronchoscopies (e.g., every 2 to 3 days) to assess progression of the airway and to diagnosis new endobronchial infections. It is recommended to aggressively treat any endobronchial infection and to decrease the steroid doses, if possible, to facilitate airway healing.[11] Patients with evidence of airway necrosis should have adequate anti-fungal prophylaxis, including both systemic and inhaled anti-fungal agents.

More extensive necrosis may be treated by placement of a covered or uncovered self-expanding metallic stent during flexible fiber-optic or preferably rigid bronchoscopy. Uncovered stents may facilitate healing by stimulating

neo-epithelialization, whereas covered stents may help seal areas of dehiscence.[14,67–70] It is critical to avoid sheer stress during stent placement, which would risk airway disruption. Self-expanding stents that are positioned at the correct depth and then allowed to expand are preferred. These exert a nearly pure radial force and minimize the risk of disruption. Stents are usually removed after healing of the area of necrosis, which usually takes about 6 to 8 weeks. However, stent placement remains controversial.

It has been the practice in many centers to undertake conservative management due to the potential risks associated with stents, including migration, in-stent stenosis due to excessive granulation tissue formation, and the potential increased risk of secondary infections.[67–69] Removal of the stent may also be hazardous, particularly with uncovered stents (which allow granulation tissue ingrowth), resulting in trauma, bleeding, and anastomotic disruption. There is additional theoretical concern that a polyurethane covered stent may promote bacterial colonization and airway infection.

Silicone stents have typically been avoided as they do not promote neo-epithelialization and the sheer force required for silicone stent placement may enlarge the defect.[68] In patients with partial dehiscence, repair may be attempted using bronchoscopic application of fibrin glue or α-cyanoacrylate glue, sometimes with interval stent placement.[70] However, there is little experience regarding the efficacy of this strategy in lung transplant patients and only a few published case reports. Most low-grade partial dehiscence will heal in the absence of local complications such as abscess formation, but a proportion of patients may go on to develop anastomotic strictures, excessive granulation tissue, or bronchomalacia.[67–69]

Patients with severe dehiscence or those who fail to respond to more conservative measures may be considered for open surgical repair or re-anastomosis of the bronchus. In these situations, however, there is usually ongoing airway ischemia, sepsis, and critical illness. Re-anastomosis of the airway is therefore challenging due to poor quality tissue and the presence of local inflammation, ischemia, and infection. Supporting and augmenting the repaired anastomosis with a peri-cardial, intercostal muscle, or omental flap may be required given the adverse conditions for healing.[71–73] There have been anecdotal institutional successes with the use of pedicled intercostal muscle flaps that can be wrapped around the bronchial anastomosis to encourage neo-vascularization and resist infection. However, there has been an isolated case report of ossification at the level of the harvested periosteum of an intercostal muscle flap, which led to bronchial stenosis.[72] Smaller defects may be closed primarily with the addition of peri-cardial buttresses or autologous tissue pledgets to aid in securing friable tissue, although small defects may often heal spontaneously over time without intervention. Aortic homografts have been used to close larger defects arising from dehiscence.[73] Overall, reconstructive surgical approaches to dehiscence have been both challenging and disappointing.

If conservative and endoscopic management of a dehiscence is not successful, resection strategies may be deployed as a last resort. If the patient's respiratory status is favorable, and in the absence of severe pleural space infection, allograft pneumonectomy may be considered. Ischemia of the bronchial stump and local infection are a concern and coverage of the stump with a vascularized flap is recommended.[71–73] Retransplantation may be considered as an option but organ availability and the clinical status of the patient, particularly with sepsis, may preclude this as a viable option.

Stenosis

Despite the high prevalence of this complication, there have been no randomized, controlled trials examining treatment of post-transplant stenosis, and the best available evidence is from case series and expert opinion. Patients are often selected for various treatment approaches based on the appearance and location of the airway stenosis, as well as local availability of techniques and expertise.

Treatment strategies often employ balloon dilation, endobronchial stent placement, laser therapy, electrocautery, argon plasma coagulation, and cryotherapy.[8,14,18,60,62–65,74–78] These can be performed as isolated procedures or often in combination. In rare cases, surgery may be utilized, and ultimately some patients will undergo retransplantation for refractory airway stenosis.

Balloon dilation

When airway stenosis is detected, bronchoscopic balloon dilation is often the initial step in management. Although not always effective, it is one of the least invasive techniques. In rare cases, balloon dilation alone may be sufficient to alleviate symptoms.[74] A single balloon dilation does not typically result in a durable effect, and multiple dilations must be performed at regular intervals to break the fibrous stricture at intervals dictated by the severity of clinical symptoms.[75] Balloon dilation is occasionally performed in conjunction with an endobronchial stent to maintain the expanded diameter until the airway remodels.[11,14,62,74,75]

Endobronchial stent insertion

Endobronchial stent placement is the most extensively described intervention reported for management of airway stenosis in lung transplant recipients. Several single-center case series have been published, but with a number of limitations, including small patient cohorts, and no clear consensus on placement, timing, or stent management.[17,25,29,39,62,63,75–77] Based on the risk associated with bronchial stents in lung transplant recipients, stent placement should be avoided if possible, and should only be considered in symptomatic patients requiring frequent balloon dilations (i.e., 2 or more dilations a month) and can confirm symptomatic improvement with balloon dilation.

Ablative therapies: Laser therapy/endobronchial electrosurgery/argon–plasma coagulation/cryotherapy

Airway stenosis due to granulation tissue or webs may benefit from various techniques of airway debridement.

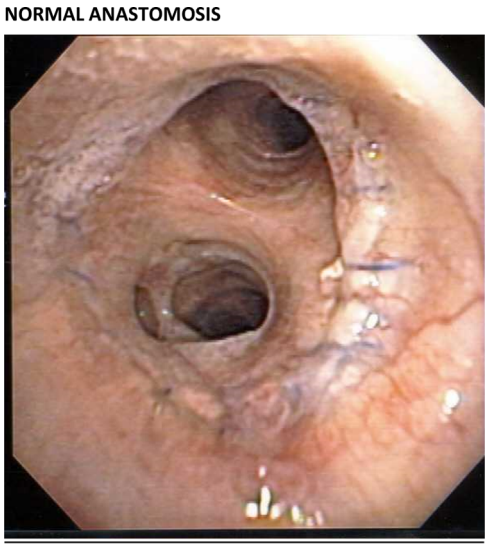

Figure 1 Location a: The airway ischemia and/or necrosis location is perianastomotic within 1 cm of the anastomosis, Extent a: Airway ischemia affects <50% of the anastomotic circumferential.

These approaches may be less useful for fibrotic strictures where it is difficult differentiate excess intraluminal tissue from the airway wall. Laser surgery, endobronchial electrosurgery (EES), and argon–plasma coagulation (APC) result in immediate restoration of luminal patency, in contrast to the more delayed effects of cryotherapy or brachytherapy.

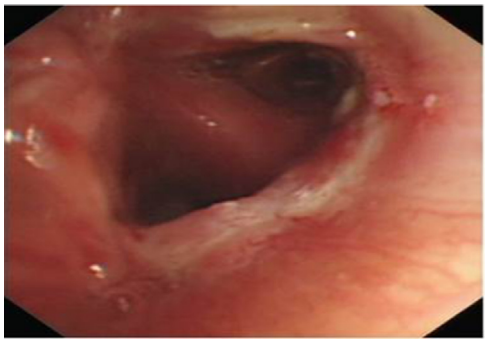

Figure 2 Location a: The airway ischemia and/or necrosis location is perianastomotic within 1 cm of the anastomosis, Extent b: Airway ischemia affects 50-100% of the anastomotic circumferential.

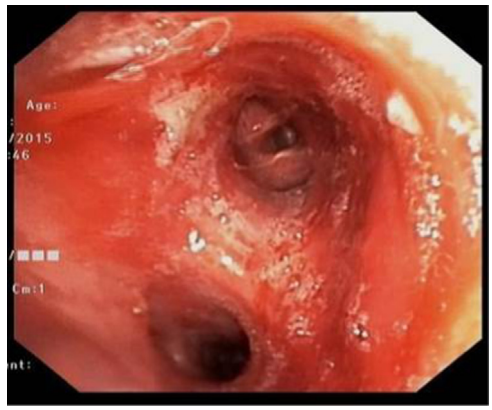

Figure 3 Location b: The airway ischemia and/or necrosis extends >1 cm from the anastomosis to major airways, Extent b: Airway ischemia affects 50-100% of the anastomotic circumferential.

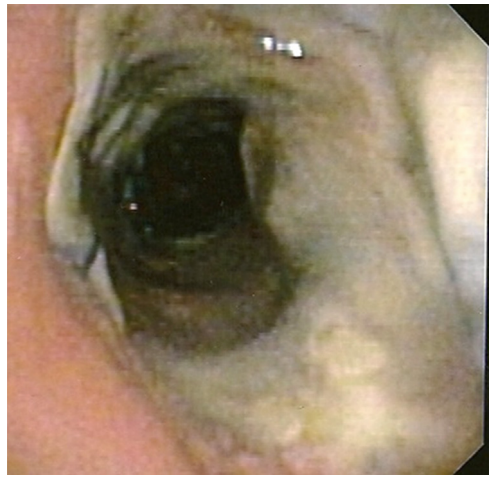

Figure 4 Location c: The airway ischemia and/or necrosis extends > 1cm from the anastomosis into the lobar or segmental airways, Extent b: Airway ischemia affects 50-100% of the anastomotic circumferential.

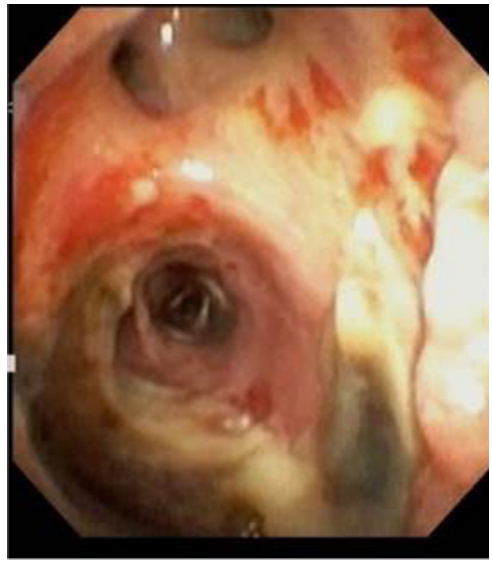

Figure 5 Location a: The airway ischemia and/or necrosis location is perianastomotic within 1 cm of the anastomosis Extent c. Airway necrosis affecting <50% of the anastomotic circumferential.

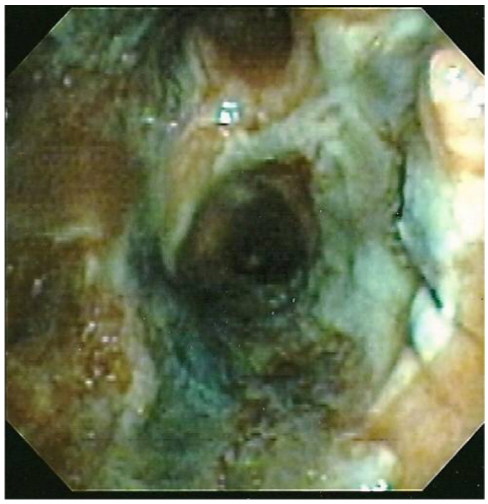

Figure 6 Location b: The airway ischemia/necrosis location is >1 cm from the anastomosis to major airways including Bronchus Intermedius Extent d: Airway necrosis affecting 50-100% of the anastomotic circumferential.

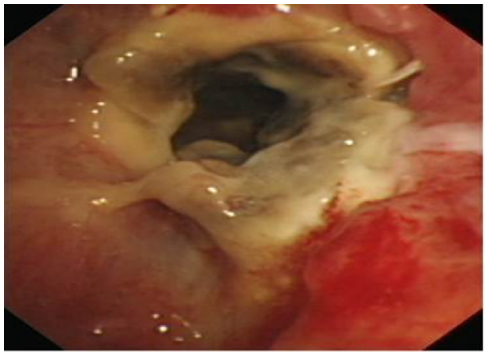

Figure 7 Location b: The airway ischemia/necrosis location is >1 cm from the anastomosis to major airways including Bronchus Intermedius Extent d: Airway necrosis affecting 50-100% of the anastomotic circumferential.

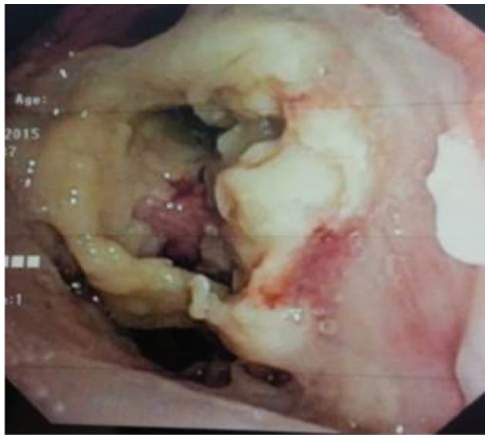

Figure 8 Location c: The airway ischemia/necrosis location is >1 cm from the anastomosis into lobar or segmental airways Extent d: Airway necrosis affecting 50-100% of the anastomotic circumferential.

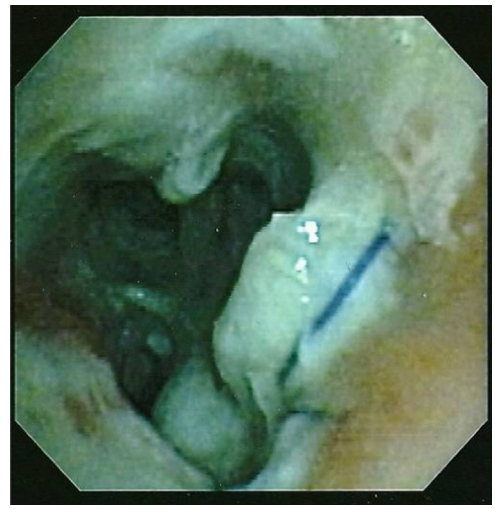

Figure 9 Location c: The airway ischemia/necrosis location is >1 cm from the anastomosis into lobar or segmental airways Extent d: Airway necrosis affecting 50-100% of the anastomotic circumferential.

DEHISCENCE (D)

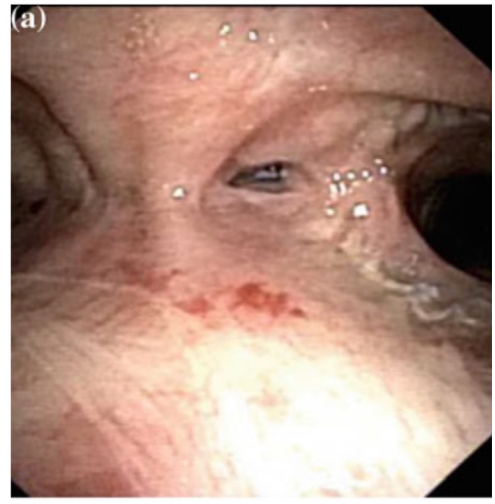

Figure 10 Location a: The anastomosis dehiscence is at the cartilaginous wall, Extent a: The extension of the dehiscence is 0-25% of the anastomotic circumference.

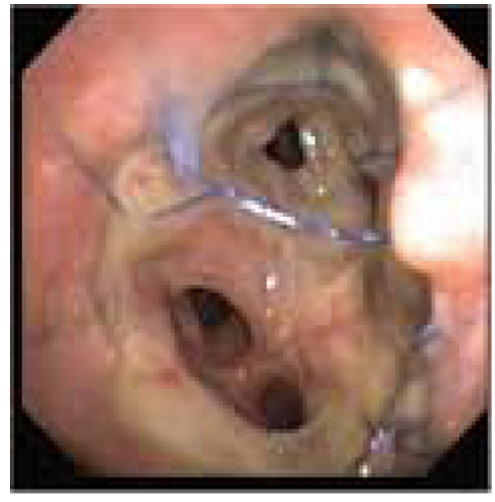

Figure 11 Location a: The anastomosis dehiscence is at the cartilaginous wall, Extent b: The extension of the dehiscence is > 25-50% of the anastomotic circumference.

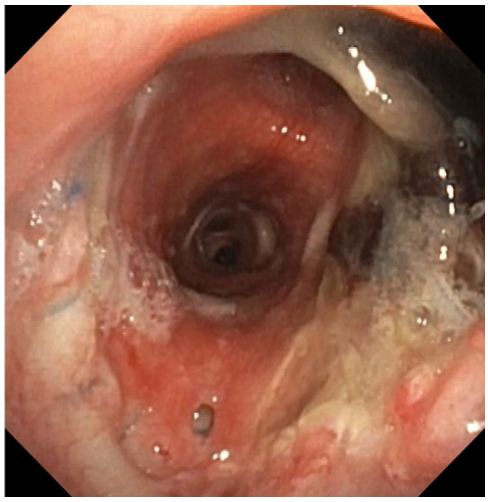

Figure 12 Location b: The anastomosis dehiscence is at the membranous wall, Extent a: The extension of the dehiscence is 0-25% of the anastomotic circumference.

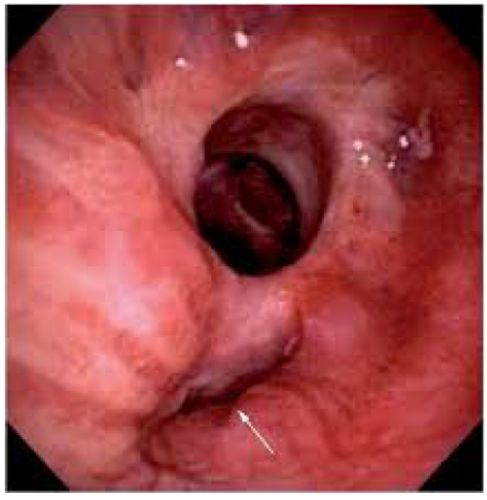

Figure 13 Location b: The anastomosis dehiscence is at the membranous wall, Extent b: The extension of the dehiscence is >25-50% of the anastomotic circumference.

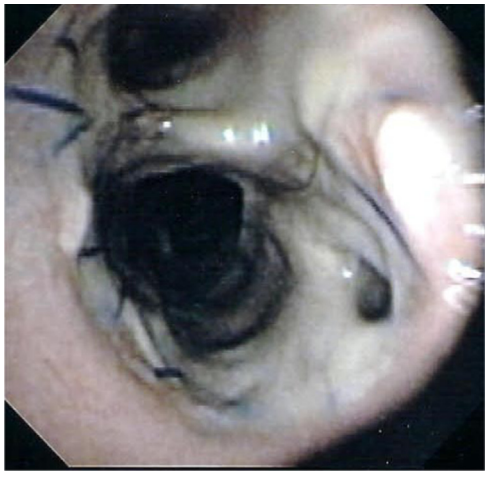

Figure 14 Location b: The anastomosis dehiscence is at the membranous wall Extent b: The extension of the dehiscence is >25-50% of the anastomotic circumference.

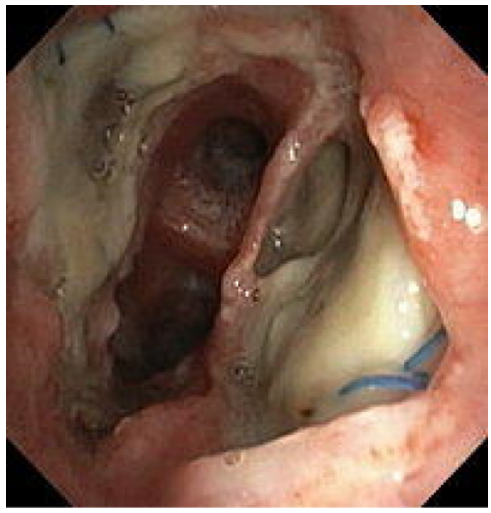

Figure 15 Location b: The anastomosis dehiscence is at the membranous wall, Extent d: The extension of the dehiscence is >50-75% of the anastomotic circumference.

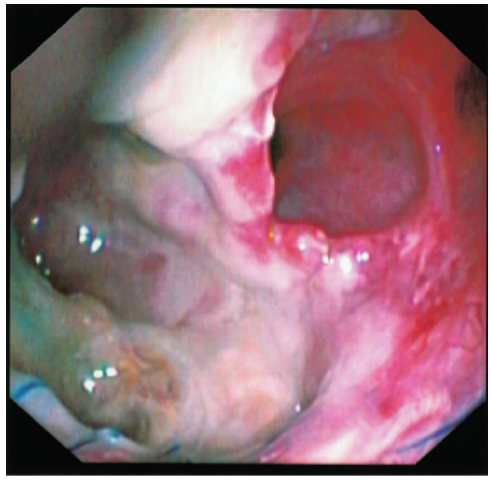

Figure 16 Location c: The anastomosis dehiscence involves the membranous and cartilaginous wall, Extent d: The extension of the dehiscence is >75% of the anastomotic circumference.

STENOSIS (S)

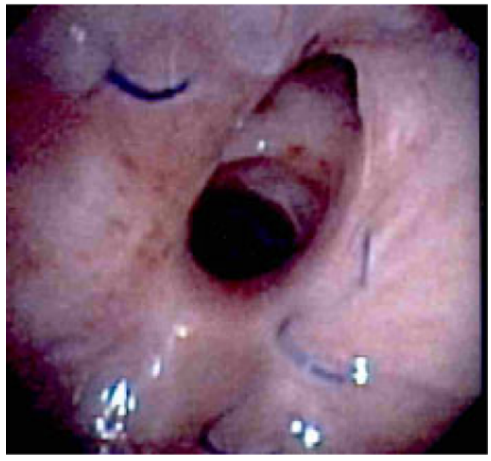

Figure 17 Location a: The stenosis is at the anastomotic site, Extend a: There is a 0-25% reduction in cross-sectional area.

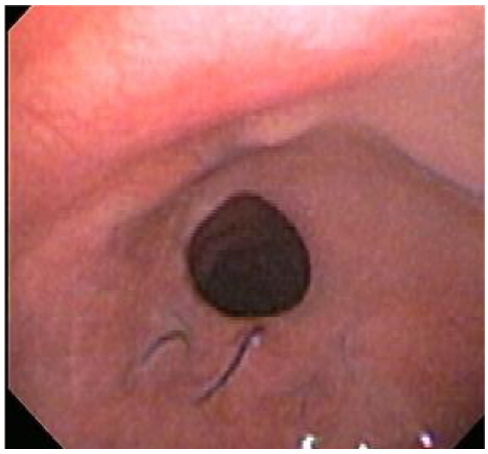

Figure 18 Location a: The stenosis is at the anastomotic site, Extent b: There is a >25-50% reduction in cross-sectional area.

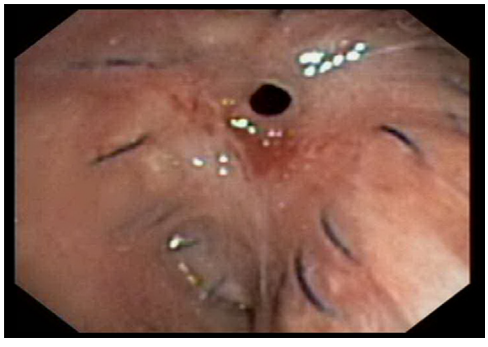

Figure 19 Location a: The stenosis is at the anastomotic site, Extent c: There is a >50 but <100% reduction in cross-sectional area.

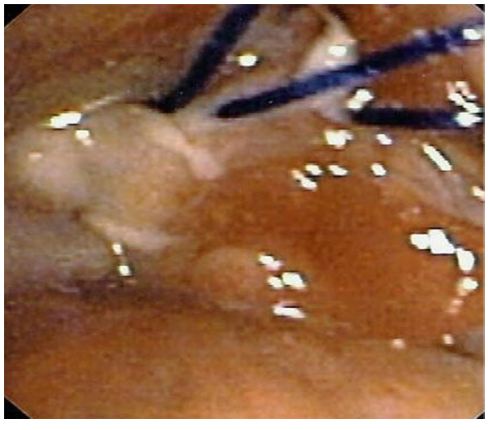

Figure 20 Location a: The stenosis is at the anastomotic site Extent d: There is 100% reduction in cross-sectional area.

Cryotherapy has been utilized in the management of lung transplant recipients with airway stenosis.[78]

Brachytherapy

Brachytherapy can be considered as an option when airway stenosis is secondary to hyperplastic tissue in the airway.

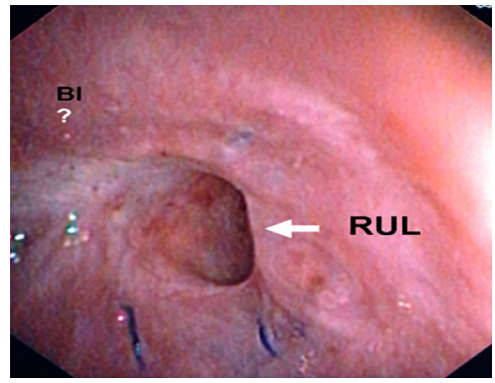

Figure 21 Location b: The stenosis is at the anastomotic and lobar/segmental site (Bronchus intermedius), Extent d: There is 100% reduction in cross-sectional area.

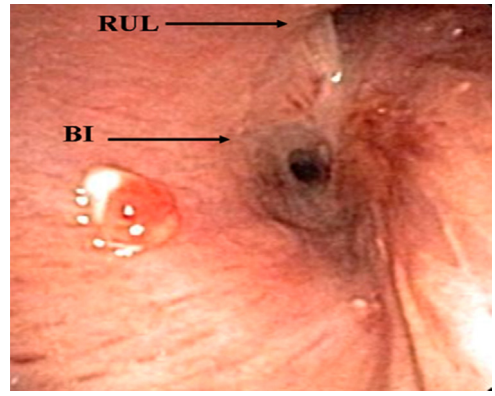

Figure 22 Location b: The stenosis is at the anastomotic and lobar/segmental site (Bronchus intermedius), Extent c: There is a >50 but <100% reduction in cross-sectional area.

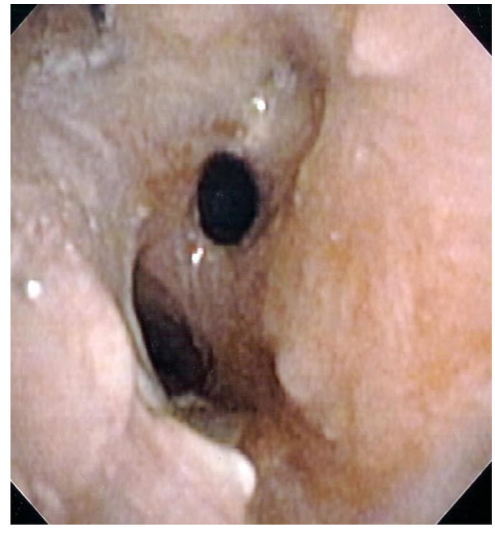

Figure 23 Location c: The stenosis is at the lobar/segmental site only, Extent b: There is a >25-50% reduction in cross-sectional area.

Several centers have reported the successful use of high-dose rate (HDR) endobronchial brachytherapy for airway stenosis, particularly in patients who failed to achieve durable improvement after intervention with multiple ablative techniques.[79–81]

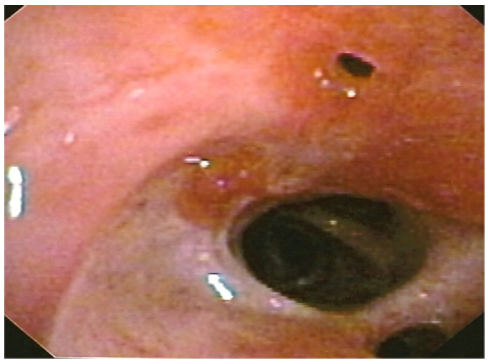

Figure 24 Location c: The stenosis is at the lobar/segmental site only (RML stenosis), Extent c: There is a >50 but $<100\%$ reduction in cross-sectional area.

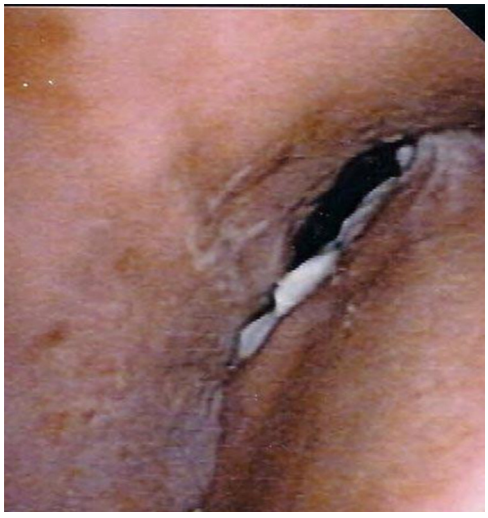

Figure 25 Ma: The malacia is perianastomotic-within 1 cm of the anastomosis.

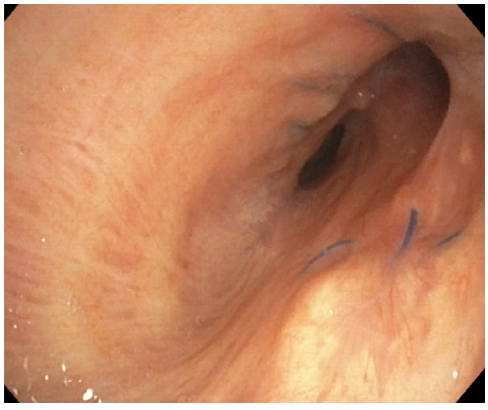

Figure 26 Mb: The malacia is diffuse, involving the anastomosis and extending beyond 1 cm.

Other therapies: Mitomycin C

There have been some case reports using endobronchial mitomycin C application for control of recurrent airway stenosis with good results after lung transplantation.[82,83] However, efficacy and safety remain unclear in this population. There is a paucity of evidence or clinical trials to support this as a standard treatment of airway stenosis.

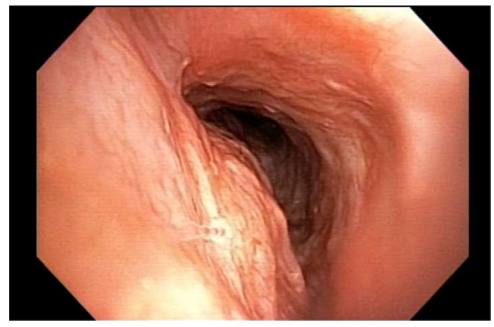

Figure 27 Mb: The malacia is diffuse, involving the anastomosis and extending beyond 1 cm, OTHER ENDOBRONCHIAL PATHOLOGY: presenting as necrosis and stricture in the airway.

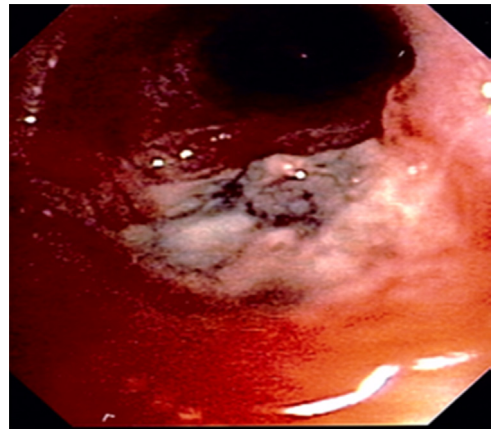

Figure 28 Endobronchial Aspergillosis at the right anastomosis.

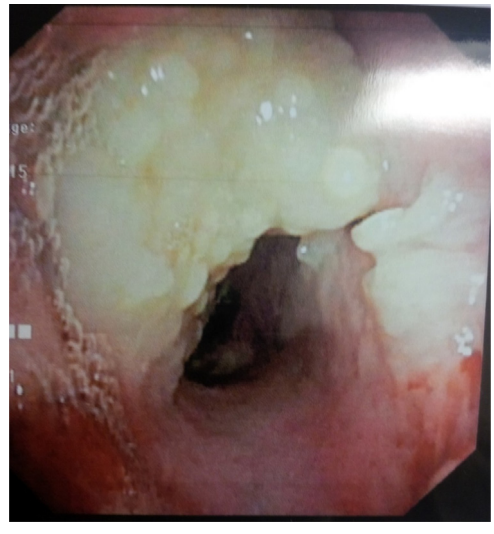

Figure 29 Endobronchial post-transplant lymphoproliferative disorder (PTLD) involving the left anastomosis.

Surgical intervention

Surgical resection is typically not the preferred approach for the management of recalcitrant airway stenosis due to

several factors, including the immunosuppressed status of the recipient, long-term steroid use, and post-surgical adhesions. However, several authors have reported cases in which surgery has been performed for refractory airway stenosis.[84–87] Multiple surgical procedures have been described, including lower sleeve bilobectomy, wedge bronchoplasty of the bronchus intermedius, and isolated sleeve resection of the bronchus intermedius.[84–87]

Malacia

Tracheobronchomalacia (TBM) management represents a therapeutic challenge, as there is no established consensus regarding treatment. Management strategies range from conservative therapy (pulmonary hygiene and non-invasive positive pressure ventilation [NIPPV]) to invasive therapy (silicone airway stents and tracheobronchoplasty).[88–97] Because the primary goal of therapy is to improve symptoms and quality of life, asymptomatic malacia should not be treated. Treatment of the underlying cause should be considered first. If symptoms improve, monitoring without further treatment is recommended.

In critically ill patients, such as those who require airway stabilization to be weaned off ventilatory support, placement of an airway stent may be considered. If the patient is not critically ill, NIPPV is an initial treatment option. Positive airway pressure therapy has been shown to improve dyspnea, cough, and secretion management in selected patients with TBM.[89–91] NIPPV acts as a pneumatic stent by increasing intraluminal pressure.[89–91] Its benefits may be due to improved airway stiffness, increased lung volumes, or decreased work of breathing. The amount of pressure required can be determined by performing a dynamic bronchoscopy while titrating NIPPV settings.[92] NIPPV can be used at night and intermittently as needed during the day.

If a patient has severe symptoms or functional impairment that fails to improve with conservative treatment, airway stenting or surgical correction may be considered. However, if expiratory airflow-limiting segments are not within the central airway (i.e., diffuse or peripheral), stenting and surgery should not be offered. Stents act to restore airway patency and improve secretion clearance. Some observational studies have demonstrated improved symptoms and quality of life with short-term stenting.[75–77,93,94] In a small series of 4 patients, stent placement for transplant-related bronchomalacia improved spirometry.[75] Removable/silicone stents are preferred in benign disease and are placed via flexible or rigid bronchoscopy. Close surveillance is required, as long-term use has been associated with a high rate of stent-related complications, notably migration and obstruction.[75–77,93,94]

Surgery may be an option for operable candidates who improve after a stent trial (10 to 14 days). Surgical approaches include resection, reconstruction, and tracheoplasty.[95–97] Tracheoplasty is a surgical form of airway splinting using a mesh, which reshapes the airway wall and reinforces the membranous portion of the trachea. Favorable outcomes have been seen in several uncontrolled trials.[95,96] Although good outcomes have also been seen with resection of focal malacia, care must be taken before committing patients to invasive and potentially harmful procedures.[97] If the patient is not a surgical candidate, a permanent stent can be considered, although this also needs to be balanced with the associated risk of stent-related adverse effects.

Conclusion

Airway complications are a major source of post–lung transplant morbidity. The proposed grading system is intended to provide a unified system of assessment and measurement that allows for a standardized description of endoscopic changes as the airways evolve through the early and late stages of healing. A universally accepted grading system is the first step in providing a more nuanced understanding of airway complications by facilitating precise scientific communication. It is a necessary step in defining the prevalence and consequences of airway abnormalities, and will enable the creation of management strategies based on data that is readily translated across institutions. This grading system also lays the foundation for an international airway complication registry to enhance collaboration and possibly facilitate prospective multicenter studies to increase the speed of discovery within the field of airway complications after lung transplantation Figs. 1–29.

Disclosure statement

The authors have no conflicts of interest to disclose.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at www.jhltonline.org.

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