

Peer Review File

Article information: <https://dx.doi.org/10.21037/ccts-20-163>

Reviewer A

Comments to the authors: Overall the authors present a clear and concisely written review about anastomotic airway complications after lung transplantation. Although some other review papers about this subject have been published, the topic of the study is of interest for the transplant community.

Comment 1: Some of the major references used to describe the incidence of bronchial complications in the introduction are from 1997-2009. Since then, other studies have been published and should be included.

Response 1: Thank you for the comment. We removed the oldest reference from 1997 and included more recent references from 2011 and 2016. The introductory text was also revised to reflect the wide-ranging incidence of anastomotic airway complications across multiple studies.

Comment 2: In anatomical considerations, when the authors are describing BAR as an alternative for revascularization they should include the difficulties added to the technique as one of the downsides of using it on a regular basis.

Response 2: Thank you for the comment. We realize that BAR is not routinely performed across transplant centers because of the added technical difficulty. We felt that elaborating on the technique and challenges therein would be outside the scope of this article and our expertise since we are not thoracic surgeons.

Comment 3: In risk factors, when discussing about wrapping the anastomoses, although no prospective randomize trials have been done comparing wrapping vs not wrapping the anastomoses, some benefits have been found. Some wrapping techniques used by some centers don't increase the difficulty or time as stated by the authors.

Response 3: Thank you for the comment. We certainly appreciate the difference in experience and success with wrapping techniques among different centers. We identified one prospective trial which is cited in our review that found no difference in the incidence of anastomotic complications with wrapping versus no wrapping. Based on the available evidence, we believe the role of wrapping is of uncertain value and may add time and difficulty to the procedure.

Comment 4: In Classification of the airway complications (Bronchial stenosis), references again are around 13-20 years ago and do not mention the recently published ISHLT consensus.

Response 4: Thank you for comment. In our review, we described the timeline and evolution of the various grading systems used across the years. The last paragraph of the “classification of airway complications,” section highlights the recently proposed ISHLT consensus. We revised the text to include a summary of the ISHLT grading system.

Comment 5: Management of stenosis stenting is mentioned as an option for patients that present with recurrent stenosis, it should be added that those patients have to have confirmed symptomatic improvement after balloon dilatation.

Response 5: Thank you for the comment. We agree that repeated management of bronchial stenosis should only be direct toward patient’s who derive benefit. We revised the text as follows: “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.”

Comment 6: Dehiscence, some centers accept conservative management due to the potential risk that has been associated with stents. Silicone stents are usually avoided as they do not promote epithelization. Chest drainage should be done when signs of pneumothorax-air leak. Decreasing steroids is also done in some centers. Antibiotics and antifungal prophylaxis and treatment. Bronchoscopic topical therapies can be an option in patients with partial dehiscence. Stents are usually removed after 6-8 weeks.

Some comments could be added regarding the surgical option including the challenges of having poor quality tissue secondary to inflammation infection and ischemia. Other details about surgical approach.

Response 6: Thank you for the comment. We believe most of the above comments were highlighted in the manuscript. The details surrounding the surgical approach and technical difficulties of repairing a dehiscence are important but we felt were outside the scope of this article and our expertise.

Comment 7: A grading system should be added.

Response 7: Thank you for the comment. The ISHLT grading system is copyrighted and therefore would require permission from the authors. We revised our manuscript to include a summary of the ISHLT grading system.

Comment 8: In malacia, the management goal is to improve symptoms and quality of life of the patient, important to state that asymptomatic patients should not be treated. Also, the role that surgery may have in patients who improve after stent.

Response 8: Thank you for the comment. We expanded the text to include the role of stenting and surgery for malacia.

Reviewer B

Comment 1: There is no apparent advantage in the use of non-standard abbreviations such as 'AC 'for airway complications. I suggest replacing all the abbreviation with 'airway complications' to help with flow.

Response 1: Thank you for the comment. We removed the abbreviation in the manuscript.

Comment 2: It would be more helpful for the review (and the readers) if you could provide a summary table of the 2018 consensus recommendations regarding the classification and grading of airway complications.

Response 2: Thank you for the comment. We revised the manuscript to include a summary of the ISHLT grading system.

Comment 3: There is fleeting reference to the role of spirometry and the flow-volume loop in the evaluation of airway complications. Spirometry is the gold standard tool for monitoring of patients post-lung transplant. While scant attention is usually paid to the flow-volume loop by lung transplant practitioners, the flow-volume loop often imparts a lot of information regarding the presence and site of airway stenosis and malacia. At minimum, a paragraph about the role and limitation of spirometry and a figure with characteristics findings in patients with significant airway stenosis and bronchomalacia should be included in the review.

Response 3: Thank you for the comment. We wholeheartedly agree that spirometry is a vital tool for monitoring patients posttransplantation. In our review, we highlight the findings of various diagnostic tools including spirometry, chest imaging and bronchoscopy. While spirometry may provide clues to the diagnosis of malacia or stenosis, the test has its limitations, including false positive and negative results. In many instances, the diagnosis is uncovered during routine imaging or surveillance bronchoscopy. Moreover, if the diagnosis of malacia or stenosis is suspected then confirmation must be sought bronchoscopically. We believe that elaborating further on the role of spirometry in assessment of these specific complications is outside the scope of this review.

Reviewer C

Comments to the authors: This article reviews and analyzes the airway complications (ACs) after lung transplantation and the optimal endoscopic management strategies.

Comment 1: The authors elaborate the risk factors of ACs in three aspects: perioperative factors, donor and recipient factors, and immunosuppressive medications. Regarding the perioperative factors, it is focused on surgical anastomosis and perioperative infection. When describing bronchial artery reconstruction, it is recommended to briefly introduce the reconstruction methods. It would be better to present the current international mainstream modalities for

anastomosis technique and length of donor-recipient bronchial anastomosis, which would offer the readers a clear contrast. If different complications occur after using the same modality, it indicates that ACs are more likely to relate to other factors, which may help the readers choose a more optimized surgical anastomosis plan.

Response 1: Thank you for the comment. In our review, we sought to provide a general overview of the most common perioperative risk factors for anastomotic airway complications. A more in-depth description of the various surgical techniques including BAR is outside the scope of this review and our expertise.

Comment 2: The authors have presented the classification of airway complications after lung transplantation. The suggestion is to present it in the following order: 1) Regional ischemic necrosis; 2) Infection; 3) Dehiscence or fistula; 4) Tracheobronchomalacia; 5) Bronchial stenosis. Anastomotic complications after lung transplantation usually occur successively. First, the mismatch between the donor and the recipient or the excessive cold ischemia time causes the lung transplantation ischemia-reperfusion injury in the early postoperative period, which stimulates PDG, and then results in regional anastomotic ischemic necrosis. Consequently, regional anastomotic ischemic necrosis leads to sloughing of local tracheal mucosa and failure of mucus clearance that generates sputum callus which is prone to be complicated by fungal infection, and likely to further bring about early anastomotic dehiscence and local fistula. The anastomosis will gradually heal if appropriate treatment is provided at this time. But local tracheomalacia or long-term local stenosis may occur at the anastomosis site afterwards. In summary, anastomotic complications are successive, so the classification can be presented in the order of complication occurrence as mentioned above.

Response 3: Thank you for the comment. We reorganized the listing of each airway complication to align with the above comments.

Comment 3: In terms of treatment plan for anastomotic stenosis, the first choice in our center is local treatment, balloon dilatation, incision and expansion of the tracheal stenosis, and cryotherapy combined with balloon dilatation. If there is no improvement after continuous treatment, we may opt to implant a self-expandable

metallic stent using a flexible bronchoscope for the short term, and remove it subsequently within two months when the symptoms of airway stenosis or malacia are improved (the removal of the metallic stent would be much challenging after two months). Rigid stents and silicone stents have their advantages, but their disadvantages such as easy displacement and poor sputum expectoration may cause problems in postoperative airway management.

Response 3: Thank you for the comment. We largely agree with the management plan as outlined above. Initially, we opt to manage patients conservatively with ablative techniques and balloon dilation as indicated. If symptomatic stenoses are rapidly recurring and benefited from prior endoscopic treatment then stenting is usually offered. The type of stent chosen varies, but we typically begin with a SEMS to promote conformational changes in the airway shape, after which the stent is removed (usually around 2-3 months). If stenting is still required beyond the first few months then we often place a silicone stent.