Review Article on Lung Transplantation: Past, Present, and Future

Management of chronic rejection after lung transplantation

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Abstract: Outcomes after lung transplantation are limited by chronic lung allograft dysfunction (CLAD). The incidence of CLAD is high, and its clinical course tends to be progressive over time, culminating in graft failure and death. Indeed, CLAD is the leading cause of death beyond the first year after lung transplantation. Therapy for CLAD has been limited by a lack of high-quality studies to guide management. In this review, we will discuss the diagnosis of CLAD in light of the recent changes to definitions and will discuss the current clinical evidence available for treatment. Recently, the diagnosis of CLAD has been subdivided into bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS). The current evidence for treatment of CLAD mainly revolves around treatment of BOS with more limited data existing for RAS. The best supported treatment to date for CLAD is the macrolide antibiotic azithromycin which has been associated with a small improvement in lung function in a minority of patients. Other therapies that have more limited data include switching immunosuppression from cyclosporine to tacrolimus, fundoplication for gastroesophageal reflux, montelukast, extracorporeal photopheresis (ECP), aerosolized cyclosporine, cytolytic anti-lymphocyte therapies, total lymphoid irradiation (TLI) and the antifibrotic agent pirfenidone. Most of these treatments are supported by case series and observational studies. Finally, we will discuss the role of retransplantation for CLAD.

Keywords: Chronic rejection; chronic lung allograft dysfunction; bronchiolitis obliterans syndrome; restrictive allograft syndrome

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Introduction

Long term outcomes after lung transplantation are limited by chronic allograft dysfunction, and allograft failure is the leading cause of death beyond the first year after transplantation (1). The understanding of the phenotypes and pathophysiology of chronic lung allograft dysfunction has evolved over time. The first described form of chronic rejection was termed bronchiolitis obliterans syndrome (BOS) by Cooper *et al.* in 1993. Obliterative bronchiolitis was recognized as the histologic hallmark of chronic rejection, but because of difficulty establishing the diagnosis histologically with transbronchial lung biopsies, BOS, defined according to changes in spirometry was accepted as the clinical surrogate (2). BOS was defined as a persistent decrement in forced expiratory volume in 1 second (FEV_1) ≥20% of the reference FEV_1 which is defined as the mean of the 2 highest post-transplant measurements at least 3 weeks apart (2). In the most recent International Society for Heart and Lung Transplantation (ISHLT) Registry Report, 8.5% of lung recipients developed BOS within 1 year of transplantation. This increases to 41% and 67% among 5- and 10-year survivors, respectively (3). Over the past 10 years, a different phenotype of chronic rejection with a restrictive ventilatory defect and interstitial opacities on imaging studies has been identified; this was initially

described by Sato *et al.* in 2011 and has been termed restrictive allograft syndrome (RAS) (4). The initial report described a cohort of patients who developed a persistent restrictive ventilatory defect, defined as a ≥10% decrease in total lung capacity compared with the mean of the 2 highest post-operative values and interstitial opacities on chest imaging (4). Importantly, those with RAS had significantly worse survival than those with BOS (4). Since the initial report, several other groups have described this phenotype characterized by a restrictive ventilatory defect and radiographic opacities and reported incidences between 25–37% depending on the exact definition used (5-7). Again, those with RAS have consistently had worse survival than those with BOS.

Chronic lung allograft dysfunction (CLAD) is the term currently used to describe persistent deterioration in lung function characteristic of chronic rejection. Recently, new consensus definitions for CLAD have been developed by the Pulmonary Council of the ISHLT to clarify the terminology and diagnosis (8). Based on this, definite CLAD is defined as a decline in FEV_1 ≥20% from the reference FEV_1 value which persists in spite of investigation and treatment of secondary causes of allograft dysfunction such as infection, acute rejection or airway stenosis for 3 months. Patients who have had a decline for under 3 weeks are under the category of possible CLAD and those who have had a decline between 3 weeks and 3 months are under the category probable CLAD. CLAD is staged based on changes in FEV_1 with CLAD 0 defined as FEV_1 >80% of baseline, CLAD 1 defined as FEV_1 >65–80%, CLAD 2 defined as FEV_1 >50–65%, CLAD 3 defined as FEV_1 >35–50%, and CLAD 4 defined as FEV1 ≤35%. CLAD is then subdivided into BOS, RAS, mixed, or undefined. BOS is defined as having CLAD with obstruction on spirometry defined as FEV_1/FVC <0.7, absence of restriction defined as TLC decline of <10% and absence of opacities on chest imaging. RAS is defined as CLAD with absence of obstruction, presence of restriction defined as TLC decline ≥10% from reference and presence of persistent opacities on chest imaging, preferably high resolution chest CT (9). Patients under the mixed category have both obstruction and restriction with CT opacities, and those in the undefined category do not fit into the groups categories (8).

Previous studies examining treatment for CLAD have focused primarily on BOS, and there are very few randomized controlled trials to guide management. This review will present the evidence supporting the common treatment options. *Table 1* summarizes the various treatment options discussed in detail in this review.

Azithromycin

Azithromycin is one of the few treatments for BOS that is supported by evidence from a randomized controlled trial. Initial experience with azithromycin was first reported by Gerhardt *et al.* in a 2003 where six patients with BOS were started on azithromycin (loaded with 250 mg daily for five days then maintained on 250 mg three times a week) (10). In this retrospective series, five out of the six patients had significant improvement in FEV_1 over a short (mean 13.7 weeks) follow-up period (10). This led to numerous subsequent observational studies which demonstrated that a subset of patients (varying between 18–60%) respond favorably to azithromycin (11-19). One retrospective cohort study comparing patients who received azithromycin to historical controls suggested a survival benefit with azithromycin when started at BOS stage 1 but not at later stages (18). These retrospective cohort studies led to a randomized controlled trial examining the efficacy of azithromycin in patients who have BOS (20). In this single center study, 48 patients with BOS were randomized to azithromycin (250 mg on alternate days) or placebo, and treatment was continued over 12 weeks. In the intention-to-treat analysis, there was no significant difference in FEV_1 at the end of follow-up between the two groups. However, in the analysis of those who completed the study and the post-hoc "as treated" analysis, the azithromycin group had significantly higher FEV_1 measurements than the placebo group. Furthermore, 39% (9/23) of the patients in the intention-to-treat analysis had ≥10% improvement in FEV_1, compared to none of the placebo group (20). Some, but not all studies, have suggested that BAL neutrophilia may correlate with azithromycin response (14,16,17,20). Azithromycin may also have a role in preventing BOS development. In a randomized placebo-controlled trial, 83 patients were randomized to azithromycin 250 mg three times a week or placebo after discharge from the index hospitalization after transplantation. In the azithromycin group, 12.5% developed BOS compared to 44.2% in the control group P=0.0017 (21).

Conversion of cyclosporine to tacrolimus

While there is evidence from randomized controlled trials that tacrolimus may be superior to cyclosporine in

Table 1 Treatment options for chronic rejection after lung transplantation

Treatment	Quality of evidence	Efficacy	Side effects/toxicity
Azithromycin	1 RCT, several case series and observational studies	Improvement in FEV_1 in 18–60% of those treated (29% in RCT)	Nausea, vomiting, diarrhea
Conversion of cyclosporine to tacrolimus	Case series	Decreased rate of FEV_1 decline	Increased creatinine, hyperglycemia
Gastric fundoplication	Case series and observational studies	Improvement in FEV_1 after fundoplication	Perioperative complications, postoperative dysphagia
Montelukast	Case series, observational studies, 1 small RCT	Attenuation of FEV_1 decline	Well tolerated
Extracorporeal photopheresis	Observational Studies	Improvement in FEV_1 in 12–30%, attenuation of FEV1 decline, possible mortality benefit	Generally well tolerated, citrate reactions
Aerosolized cyclosporine	1 small RCT and case series	Lower rate of CLAD progression, possible mortality benefit	Cough, pharyngeal soreness, acute breathlessness
Cytolytic anti-lymphocyte therapies	Case series and observational studies	Improvement in FEV_1 in 40%, attenuation of FEV_1 decline	Serum sickness, cytokine release syndrome, infection
Total lymphoid irradiation	Case series and observational studies	Attenuation of FEV_1 decline	Leukopenia, infection

preventing BOS, no randomized controlled trials have been performed to evaluate the efficacy of substituting tacrolimus for cyclosporine to treat BOS (22-24). Switching maintenance immunosuppression from cyclosporine to tacrolimus has been reported in case series to slow the decline in lung function among patients with BOS (25-34). The largest of these was a multicenter case series by Sarahrudi *et al.* which examined the impact of this intervention in 134 patients who had BOS (33). After conversion, the rate of change in FEV_1 decreased from –3.7% predicted per month to –0.9% predicted per month among bilateral lung recipients and from –2.5% to –0.3% among single lung recipients (33).

Fundoplication for gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) is prevalent among lung transplant recipients and pre-existing GERD may worsen following transplantation (35,36). GERD has been implicated as a risk factor for CLAD (37-39). Treatment of GERD with proton pump inhibitors reduces acid reflux symptoms but does not appear to affect nonacid reflux or bile acid levels in bronchoalveolar lavage fluid (40). Evidence for the potential benefits of fundoplication comes from observational studies and case series. Davis *et al.* reported outcomes for 26 patients with BOS who underwent fundoplication after GERD was detected by esophageal pH probe; 16 of 26 had improvement in lung function, and 13 no longer met the diagnostic criteria for BOS (41). Similar observational evidence from Hoppo *et al.* showed that 20 of 22 patients had improvement in FEV_1 after fundoplication (42). Early fundoplication may also reduce the risk of developing BOS (43,44).

Montelukast

Montelukast is a cysteinyl leukotriene receptor antagonist which has been used as a treatment for patients with BOS. A small pilot study comparing the addition of montelukast (10 mg daily) in patients with BOS and BAL neutrophil percentage <15% who were already being treated or concurrently being started on azithromycin compared to retrospectively selected control patients. Treatment with montelukast was associated with a significant decrease in the rate of FEV_1 decline compared to the control group (45). A small randomized placebo-controlled trial examined the role of montelukast in patients with late-

onset (>2 years post-transplant) BOS (46). There was no significant difference in the primary outcome of graft loss 1 year after randomization between montelukast and placebo, but in a post-hoc analysis of patients with BOS stage 1 at randomization, montelukast attenuated the rate of decline in FEV_1 (46). A subsequent larger retrospective study analyzed 153 patients with CLAD (75% with BOS and 25% with RAS) who were treated with montelukast (47). Montelukast was associated with an attenuation of FEV_1 decline after 3 and 6 months. Not surprisingly, patients who had improvement or stabilization in FEV_1 (81%) had significantly better progression-free and overall survival compared to non-responders, and patients with RAS were less likely to respond than those with BOS (47).

Extracorporeal photopheresis

Extracorporeal photopheresis (ECP) is a cell-based immunomodulatory therapy which involves leukopheresis to isolate leukocytes followed by treatment with methoxsalen and ultraviolet light, then returning the cells to the patient (48). Data for the efficacy of ECP in patients with BOS comes from multiple retrospective studies and one prospective trial. Multiple single arm before and after observational studies have shown a decrease in the rate of decline of FEV_1 after the initiation of ECP (49-51). Importantly, 12% to 25% of patients had an improvement in FEV_1 after the initiation of ECP (49-51). Two retrospective analyses had comparator arms. The first study compared 48 patients treated with ECP with 58 control patients treated with the center's standard of care (51). The rate of FEV_1 decline was lower among those treated with ECP; however, those who had RAS were less likely to respond to ECP (51). A small study compared patients with refractory BOS who were treated with ECP (n=17) to those treated with alemtuzumab (n=14) and found a significant decrease in the rate of FEV_1 decline in both groups compared to baseline, but there was no difference in the rate of FEV_1 decline between the two groups although the study was likely underpowered to detect a statistically significant difference (52). A prospective study examined the efficacy of ECP in patients with BOS (53). In this single-center, open-label nonrandomized study, 51 patients who developed BOS were treated with ECP and their outcomes were compared to 143 treated with maintenance immunosuppression. Patients were treated with ECP every 2 weeks for 3 months then every 4 weeks for 6 or 12 months depending on their response. Overall, 61% responded favorably: 30% had an improvement in FEV_1 and 31% stabilized. In addition, those treated with ECP had significantly better survival. Specifically, those with early onset BOS (within 3 years of transplantation) were more likely to respond to ECP and had better survival (53). The optimal duration of ECP is not known, but one study showed a significant decline in FEV_1 after discontinuation of ECP associated with a 58% 1-year mortality (54). Currently, there are 2 multicenter trials in the US examining the efficacy of ECP in BOS (NCT02181257). One study is a randomized-controlled trial of ECP *vs.* standard of care in patients with newly diagnosed BOS, and the other study is a single-arm observational registry of patients treated with ECP for refractory BOS.

Aerosolized cyclosporine

Inhaled cyclosporine uses the theoretical advantage of delivering relatively high-dose immunosuppression to the small airways that are affected by BOS. Initial case reports suggested stabilization in lung function and a possible survival benefit (55,56).

A randomized placebo-controlled trial examined the role of inhaled cyclosporine in the prevention of acute rejection (57). Although there was no significant difference in the incidence of acute rejection, the inhaled cyclosporine group had improved BOS-free and overall survival (57). A subsequent open label phase IIb randomized-controlled trial was conducted to evaluate the efficacy of inhaled liposomal cyclosporine on patients with established BOS; 21 patients with BOS stage 1 or 2 were randomized to inhaled cyclosporine (11 patients) or standard of care (10 patients). Those randomized to inhaled cyclosporine had better BOS progression-free survival, but this was not statistically significant (82% *vs.* 50%, P=0.1). The inhaled cyclosporine group was less likely to have BOS progression (18% *vs.* 60%, P=0.05). Secondary endpoints showed an increase in median survival in the inhaled cyclosporine group (4.1 *vs.* 2.9 years, P=0.03) and stabilization in lung function (58). There are currently two multicenter phase III trials enrolling patients with BOS to investigate the impact of inhaled liposomal cyclosporine (NCT03657342 and NCT03656926).

Cytolytic anti-lymphocyte therapies

Cytolytic therapies for CLAD including alemtuzumab, a

monoclonal antibody to CD52, and anti-thymocyte globulin result in rapid depletion of lymphocytes. Rationale for their use is to deplete the immune cells that cause chronic rejection and arrest the characteristic decline in lung function. Data supporting the use of alemtuzumab are based on case series and retrospective observational studies. One case series of 10 patients reported improvement in FEV_1 in 4 and stabilization in 3 others (59). Other uncontrolled observational studies show a decrease in the rate of FEV_1 decline after alemtuzumab (52,60). Similarly, in small uncontrolled retrospective studies, anti-thymocyte globulin has been shown to decrease the rate of FEV_1 decline (61-63). A recent retrospective study examined the impact of anti-thymocyte globulin on lung function in 108 patients who developed BOS. In this cohort, 43 (40%) patients had an improvement in FEV_1 in the 6 months after therapy while the remaining 65 (60%) had a persistent decline in FEV_1 although 47 (44%) had a decrease in the rate of FEV_1 decline (64). Treatment was associated with side-effects including serum sickness, cytokine release syndrome, and infections (64).

Total lymphoid irradiation

Total lymphoid irradiation (TLI) results in rapid and profound depletion of lymphoid cells. A few case series have reported outcomes of TLI for the management of BOS. In the first reported series, 11 patients with refractory BOS were treated with TLI but only 4 completed the full course of treatments. Those who completed treatment had a decrease in rate of FEV_1 decline that was durable (65). Subsequent series show a similar stabilization in the rate of FEV_1 decline (66-68). However, leukopenia and infections are common side-effects of TLI (65,66).

Antifibrotic therapies

Recently, there has been growing interest in the use of antifibrotic drugs for treatment of CLAD in part due to the pathologic similarities between RAS and other fibrotic lung diseases. Pirfenidone, an antifibrotic medication approved for the treatment of idiopathic pulmonary fibrosis has been studied in a case series of 11 patients with RAS and was associated with attenuation in the rate of decline in lung function (69). Currently, there are several studies investigating pirfenidone (NCT03473340, NCT02262299, and NCT03359863) and nintedanib (ClinicalTrials.gov identifier NCT03283007) as treatments for CLAD.

Re-transplantation

Re-transplantation is the only "curative treatment" for CLAD, but only a minority of patients are suitable candidates. Registry data suggest that outcomes after re-transplantation are inferior to those after primary transplantation (70). In single center observational studies, BOS-free survival was 85–90% at year 1 and 50–77% at 4–5 years. Patients who underwent re-transplantation for BOS have a higher risk of recurrent BOS and those who underwent re-transplantation for RAS have the highest risk of recurrent CLAD and worse survival (1,71,72). Clearly, re-transplantation is not an ideal therapy for CLAD for the majority of patients.

Conclusion

Chronic rejection remains the leading obstacle to better outcomes after lung transplantation largely because effective treatment has not been identified. Several treatments (e.g., ECP, anti-thymocyte globulin, azithromycin) are associated with marginal improvement in lung function in a minority of patients, but these results are not consistent. There are few randomized controlled trials to guide management, and most retrospective studies have focused on the rate of FEV_1 decline as an end point, defining a decreased rate of decline as a clinical response. This approach is subject to bias as the natural history of the decline in FEV_1 is not known and is not likely to be linear. Clearly, additional well-designed studies are needed to guide treatment decisions and improve outcomes after lung transplantation. Ideally, these would be multicenter randomized controlled trials.

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References

1. Meyer KC, Raghu G, Verleden GM, et al. ISHLT/ATS/ERS BOS Task Force Committee; ISHLT/ATS/ERS BOS Task Force Committee. An international ISHLT/ATS/ERS clinical practice guideline: diagnosis and management of bronchiolitis obliterans syndrome. Eur Respir J 2014;44:1479-503
2. Cooper JD, Billingham M, Egan T, et al. A working formulation for the standardization of nomenclature and for clinical staging of chronic dysfunction in lung allografts. J Heart Lung Transplant 1993;12:713-6.
3. Chambers DC, Cherikh WS, Harhay M, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult lung and heart-lung transplantation Report—2019; Focus theme: Donor and recipient size match. J. Heart Lung Transplant 2019;38:1042-55.
4. Sato M, Waddell TK, Wagnetz U, et al. Restrictive allograft syndrome (RAS): a novel form of chronic lung allograft dysfunction. J Heart Lung Transplant 2011;30:735-42.
5. Verleden SE, Ruttens D, Vandermeulen E, et al. Restrictive chronic lung allograft dysfunction: where are we now? J. Heart Lung Transplant 2015;34:625-30.
6. Koutsokera A, Royer PJ, Antonietti JP, et al. Development of a Multivariate Prediction Model for Early-Onset Bronchiolitis Obliterans Syndrome and Restrictive Allograft Syndrome in Lung Transplantation. Front Med (Lausanne) 2017;4:109.
7. Paraskeva M, McLean C, Ellis S, et al. Acute fibrinoid organizing pneumonia after lung transplantation. Am J Respir Crit Care Med 2013;187:1360-8.
8. Verleden GM, Glanville AR, Lease ED, et al. Chronic lung allograft dysfunction: Definition, diagnostic criteria, and approaches to treatment-A consensus report from the Pulmonary Council of the ISHLT.J Heart Lung Transplant 2019;38:493-503.
9. Glanville AR, Verleden GM, Todd JL, et al. Chronic lung allograft dysfunction: Definition and update of restrictive allograft syndrome-A consensus report from the Pulmonary Council of the ISHLT. J Heart Lung Transplant 2019;38:483-92.
10. Gerhardt SG, McDyer JF, Girgis RE, et al. Maintenance azithromycin therapy for bronchiolitis obliterans syndrome: results of a pilot study. Am J Respir Crit Care Med 2003;168:121-5.
11. Verleden GM, Dupont LJ. Azithromycin therapy for patients with bronchiolitis obliterans syndrome after lung transplantation. Transplantation 2004;77:1465-7.
12. Yates B, Murphy DM, Forrest IA, et al. Azithromycin reverses airflow obstruction in established bronchiolitis obliterans syndrome. Am J Respir Crit Care Med 2005;172:772-5.
13. Shitrit D, Bendayan D, Gidon S, et al. Long-term azithromycin use for treatment of bronchiolitis obliterans syndrome in lung transplant recipients. J Heart Lung Transplant 2005;24:1440-3.
14. Verleden GM, Vanaudenaerde BM, Dupont LJ, et al. Azithromycin reduces airway neutrophilia and interleukin-8 in patients with bronchiolitis obliterans syndrome. Am J Respir Crit Care Med 2006;174:566-70.
15. Porhownik NR, Batobara W, Kepron W, et al. Effect of maintenance azithromycin on established bronchiolitis obliterans syndrome in lung transplant patients. Can Respir J 2008;15:199-202.
16. Gottlieb J, Szangolies J, Koehnlein T, et al. Long-term azithromycin for bronchiolitis obliterans syndrome after lung transplantation. Transplantation 2008;85:36-41.
17. Vos R, Vanaudenaerde BM, Ottevaere A, et al. Long-term azithromycin therapy for bronchiolitis obliterans syndrome: divide and conquer? J Heart Lung Transplant 2010;29:1358-68.

18. Jain R, Hachem RR, Morrell MR, et al. Azithromycin is associated with increased survival in lung transplant recipients with bronchiolitis obliterans syndrome. J Heart Lung Transplant 2010;29:531-7.
19. Federica M, Nadia S, Monica M, et al. Clinical and immunological evaluation of 12-month azithromycin therapy in chronic lung allograft rejection. Clin Transplant 2011;25:E381-E389.
20. Corris PA, Ryan VA, Small T, et al. A randomised controlled trial of azithromycin therapy in bronchiolitis obliterans syndrome (BOS) post lung transplantation. Thorax 2015;70:442-50.
21. Vos R, Vanaudenaerde BM, Verleden SE, et al. A randomised controlled trial of azithromycin to prevent chronic rejection after lung transplantation. Eur Respir J 2011;37:164-72.
22. Hachem RR, Yusen RD, Chakinala MM, et al. A randomized controlled trial of tacrolimus versus cyclosporine after lung transplantation. J Heart Lung Transplant 2007;26:1012-8.
23. Treede H, Glanville AR, Klepetko W, Aboyoun C, Vettorazzi E, Lama R, et al. Tacrolimus and cyclosporine have differential effects on the risk of development of bronchiolitis obliterans syndrome: Results of a prospective, randomized international trial in lung transplantation. J Heart Lung Transplant 2012;31:797-804.
24. Penninga L, Penninga EI, Møller CH, et al. Tacrolimus versus cyclosporin as primary immunosuppression for lung transplant recipients. Cochrane Database Syst Rev 2013;(5):CD008817.
25. Knoop C, Antoine M, Vachie´ry JL, et al. FK 506 rescue therapy for irreversible airway rejection in heart-lung transplant recipients: report on five cases. Transplant Proc 1994;26:3240-1.
26. Reichenspurner H, Meiser BM, Kur F, et al. First experience with FK 506 for treatment of chronic pulmonary rejection. Transplant Proc 1995;27:2009.
27. Ross DJ, Lewis MI, Kramer M, et al. FK 506 "rescue" immunosuppression for obliterative bronchiolitis after lung transplantation. Chest 1997;112:1175-9.
28. Kesten S, Chaparro C, Scavuzzo M, et al. Tacrolimus as rescue therapy for bronchiolitis obliterans syndrome. J Heart Lung Transplant 1997;16:905-912.
29. Mentzer RM Jr, Jahania MS, Lasley RD. Tacrolimus as a rescue immunosuppressant after heart and lung transplantation. The U.S. Multicenter FK506 Study Group. Transplantation 1998;65:109-13.
30. Revell MP, Lewis ME, Llewellyn-Jones CG, et al. Conservation of small-airway function by tacrolimus/cyclosporine conversion in the management of bronchiolitis obliterans following lung transplantation. J Heart Lung Transplant 2000;19:1219-23.
31. Fieguth HG, Krueger S, Wiedenmann DE, et al. Tacrolimus for treatment of bronchiolitis obliterans syndrome after unilateral and bilateral lung transplantation. Transplant Proc 2002;34:1884.
32. Cairn J, Yek T, Banner NR, et al. Time-related changes in pulmonary function after conversion to tacrolimus in bronchiolitis obliterans syndrome. J Heart Lung Transplant 2003;22:50-7.
33. Sarahrudi K, Estenne M, Corris P, et al. International experience with conversion from cyclosporine to tacrolimus for acute and chronic lung allograft rejection. J Thorac Cardiovasc Surg 2004;127:1126-32.
34. Borro JM, Bravo C, Sole´ A, et al. Conversion from cyclosporine to tacrolimus stabilizes the course of lung function in lung transplant recipients with bronchiolitis obliterans syndrome. Transplant Proc 2007;39:2416-9.
35. Basseri B, Conklin JL, Pimentel M, et al. Esophageal motor dysfunction and gastroesophageal reflux are prevalent in lung transplant candidates. Ann Thorac Surg 2010;90:1630-6.
36. Young LR, Hadjiliadis D, Davis RD, et al. Lung transplantation exacerbates gastroesophageal reflux disease. Chest 2003;124:1689-93.
37. D'Ovidio F, Mura M, Tsang M, et al. Bile acid aspiration and the development of bronchiolitis obliterans after lung transplantation. J Thorac Cardiovasc Surg 2005;129:1144-52.
38. King BJ, Iyer H, Leidi AA, et al. Gastroesophageal reflux in bronchiolitis obliterans syndrome: a new perspective. J Heart Lung Transplant 2009;28:870-5.
39. Mertens V, Blondeau K, Van Oudenhove L, et al. Bile acids aspiration reduces survival in lung transplant recipients with BOS despite azithromycin. Am J Transplant 2011;11:329-35.
40. Blondeau K, Mertens V, Vanaudenaerde BA, et al. Gastro-esophageal reflux and gastric aspiration in lung transplant patients with or without chronic rejection. Eur Respir J 2008;31:707-13.
41. Davis RD Jr, Lau CL, Eubanks S, et al. Improved lung allograft function after fundoplication in patients with gastroesophageal reflux disease undergoing lung transplantation. J Thorac Cardiovasc Surg 2003;125:533-42.
42. Hoppo T, Jarido V, Pennathur A, et al. Antireflux surgery

preserves lung function in patients with gastroesophageal reflux disease and end-stage lung disease before and after lung transplantation. Arch Surg 2011;146:1041-7.
43. Cantu E 3rd, Appel JZ 3rd, Hartwig MG, et al. J. Maxwell Chamberlain Memorial Paper. Early fundoplication prevents chronic allograft dysfunction in patients with gastroesophageal reflux disease. Ann Thorac Surg 2004;78:1142-51; discussion 1142-51.
44. Hartwig MG, Anderson DJ, Onaitis MW, et al. Fundoplication after lung transplantation prevents the allograft dysfunction associated with reflux. Ann Thorac Surg 2011;92:462-8.
45. Verleden GM, Verleden SE, Vos R, et al. Montelukast for bronchiolitis obliterans syndrome after lung transplantation: a pilot study. Transpl Int 2011;24:651-6.
46. Ruttens D, Verleden SE, Demeyer H, et al. Montelukast for bronchiolitis obliterans syndrome after lung transplantation: A randomized controlled trial. PLoS One 2018;13:e0193564.
47. Vos R, Eynde RV, Ruttens D, et al. Montelukast in chronic lung allograft dysfunction after lung transplantation. J Heart Lung Transplant 2019;38:516-27.
48. Knobler R, Berlin G, Calzavara-Pinton P, et al. Guidelines on the use of extracorporeal photopheresis.J Eur Acad Dermatol Venereol 2014;28:1-37.
49. Benden C, Speich R, Hofbauer GF, et al. Extracorporeal photopheresis after lung transplantation: a 10-year single-center experience. Transplantation 2008;86:1625-1627.41.
50. Morrell MR, Despotis GJ, Lublin DM, et al. The efficacy of photopheresis for bronchiolitis obliterans syndrome after lung transplantation. J Heart Lung Transplant 2010;29:424-431.
51. Del Fante C, Scudeller L, Oggionni T, et al. Long-term off-line extracorporeal photochemotherapy in patients with chronic lung allograft rejection not responsive to conventional treatment: a 10-year single-centre analysis. Respiration 2015;90:118-128.
52. Moniodis A, Townsend K, Rabin A, et al. Comparison of extracorporeal photopheresis and alemtuzumab for the treatment of chronic lung allograft dysfunction. J Heart Lung Transplant 2018;37:340-348.
53. Jaksch P, Scheed A, Keplinger M, et al. A prospective interventional study on the use of extracorporeal photopheresis in patients with bronchiolitis obliterans syndrome after lung transplantation. J Heart Lung Transplant 2012;31:950-957.
54. Robinson CA, Huber L, Murer C, et al. Cessation of extracorporeal photopheresis in chronic lung allograft dysfunction: effects on clinical out-come in adults. Swiss Med Wkly 2017;147:W14429.
55. Iacono AT, Keenan RJ, Duncan SR, et al. Aerosolized cyclosporine in lung recipients with refractory chronic rejection. Am J Respir Crit Care Med 1996;153:1451-5.
56. Iacono AT, Corcoran TE, Griffith BP, et al. Aerosol cyclosporin therapy in lung transplant recipients with bronchiolitis obliterans. Eur Respir J 2004;23:384-90.
57. Iacono AT, Johnson BA, Grgurich WF, et al. A randomized trial of inhaled cyclosporine in lung-transplant recipients. N Engl J Med 2006;354:141-50.
58. Iacono A, Wijesinha M, Rajagopal K, et al. A randomised single-centre trial of inhaled liposomal cyclosporine for bronchiolitis obliterans syndrome post-lung transplantation. ERJ Open Res 2019;5:00167.
59. Reams BD, Musselwhite LW, Zaas DW, et al. Alemtuzumab in the treatment of refractory acute rejection and bronchiolitis obliterans syndrome after human lung transplantation. Am J Transplant 2007;7:2802-8.
60. Ensor CR, Rihtarchik LC, Morrell MR, et al. Rescue alemtuzumab for refractory acute cellular rejection and bronchiolitis obliterans syndrome after lung transplantation. Clin Transplant 2017;31:e12899.
61. Kesten S, Rajagopalan N, Maurer J. Cytolytic therapy for the treatment of bronchiolitis obliterans syndrome following lung transplantation. Transplantation 1996;61:427-30.
62. Date H, Lynch JP, Sundaresan S, et al. The impact of cytolytic therapy on bronchiolitis obliterans syndrome. J Heart Lung Transplant 1998;17:869-75.
63. Izhakian S, Wasser WG, Fox BD, et al. Effectiveness of rabbit antithymocyte globulin in chronic lung allograft dysfunction. Transplant Proc 2016;48:2152-6.
64. January SE, Fester KA, Bain KB, et al. Rabbit antithymocyte globulin for the treatment of chronic lung allograft dysfunction. Clin Transplant 2019;33:e13708.
65. Diamond DA, Michalski JM, Lynch JP, et al. Efficacy of total lymphoid irradiation for chronic allograft rejection following bilateral lung transplantation. Int J Radiat Oncol Biol Phys 1998;41:795-800.
66. Fisher AJ, Rutherford RM, Bozzino J, et al. The safety and efficacy of total lymphoid irradiation in progressive bronchiolitis obliterans syndrome after lung transplantation. Am J Transplant 2005;5:537-43.
67. Verleden GM, Lievens Y, Dupont LJ, etal. Efficacy of total lymphoid irradiation in azithromycin nonresponsive chronic allograft rejection after lung transplantation. Transplant Proc 2009;41:1816-20.

68. Lebeer M, Kaes J, Lambrech M, et al. Total lymphoid irradiation in progressive bronchiolitis obliterans syndrome after lung transplantation: a single-center experience and review of literature. Transpl Int 2020;33:216-28.
69. Vos R, Wuyts WA, Gheysens O, et al. Pirfenidone in restrictive allograft syndrome after lung transplantation: A case series. Am J Transplant 2018;18:3045-59.
70. Benden C, Goldfarb SB, Edwards LB, et al. The registry of the International Society for Heart and Lung Transplantation: seventeenth official pediatric lung and heart-lung transplantation report--2014; focus theme: retransplantation. J Heart Lung Transplant. 2014;33:1025-33.
71. Verleden SE, Todd JL, Sato M, et al. Impact of CLAD phenotype on survival after lung retransplantation: a multicenter study. Am J Transplant 2015;15:2223-30.
72. Hall DJ, Belli EV, Gregg JA, et al. Two decades of lung retransplantation: a single-center experience. Ann Thorac Surg 2017;103:1076-83.

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