6. Lung transplantation

6.1. Induction therapy

Sweet S, et al. (2022). CTOTC-08: A multicenter randomized controlled trial of rituximab induction to reduce antibody development and improve outcomes in pediatric lung transplant recipients. American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons, 22(1), 230–244. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34599540/

- Randomized, placebo-controlled, double-blind study of pediatric LTR, hypothesizing that rituximab plus rabbit anti-thymocyte globulin induction would reduce de novo DSA development and improve outcomes. There was no difference between treatment groups in time to the primary composite outcome endpoint (death, bronchiolitis obliterans syndrome grade 0-p, obliterative bronchiolitis or listing for retransplant). A post-hoc analysis substituting more stringent chronic lung allograft dysfunction criteria for BOS 0-p showed no difference in outcome ($p = .118$). The incidence of adverse events including infection and rejection episodes was not different between groups.

Shagabayeva L, et al. (2022). Induction therapy in lung transplantation: A contemporary analysis of trends and outcomes. Clinical transplantation, e14782. Advance online publication. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35848518/

- Reviewed United Network for Organ Sharing registry of first-time, adult LTR from 2006 to 2018 to compare long term survival between induction strategies. Patients receiving basiliximab, alemtuzumab or anti-thymocyte globulin vs no induction were found to have lower long-term mortality (all $p < .05$). Utilizing propensity score matching of basiliximab vs. no induction populations demonstrated a statistically significant association with increased long- term survival and lower risk of acute rejection when using basiliximab ($p < .001$).

Furukawa M, et al. (2022). Induction Strategies in Lung Transplantation: Alemtuzumab vs. Basiliximab a Single-Center Experience. Frontiers in immunology, 13, 864545. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35720296/

- Retrospective single center review of 807 LTR between 2011-2020 comparing use of alemtuzumab vs basiliximab induction strategies. The 5 year survival rate with alemtuzumab (64.1%) was significantly higher than with basiliximab (52.3%, $p<0.001$). The alemtuzumab group also experienced less acute cellular rejection in the first year (39.1% alemtuzumab vs 53.4% basiliximab, $p<0.001$). The authors hypothesize that survival rates between induction strategies may be attributable to differences in recipient characteristics between the groups

Narula T, et al. (2021). Antithymocyte globulin is associated with a lower incidence of de novo donor-specific antibody detection in lung transplant recipients: A single-center experience. Immunity, inflammation and disease, 9(4), 1418–1427. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8589359/

- Retrospective single center review of 67 consecutive LTR between Jan 2016-Dec 2017 evaluating the use of a single dose of rabbit antithymocyte globulin (1.5 mg/kg within 24 hours of transplant) vs no induction in LTR on the development of de novo DSA. De novo HLA DSA were detected in 22/67 (32.8%) LTR within 1-year posttransplant. Of these, 9/41 (21.9%) occurred in the induction therapy group and 13/26 (50%) in the noninduction group, a significant difference ($p=.017$). HLA class II DSA were detected at a lower rate in the induction therapy group ($p=.005$). Differences in overall survival or 3-year freedom from chronic lung allograft dysfunction rates between the two groups were not statistically significant.

Kim HE, et al. (2021). Basiliximab Induction with Delayed Calcineurin Inhibitors for High-Risk Lung Transplant Candidates. Yonsei medical journal, 62(2), 164–171. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33527796/

- Retrospective single center analysis of 236 LTR between 2013-2019. Forty-one patients (17.4%) received basiliximab induction, and 195 patients (82.6%) received a routine triple-drug regimen without induction. No significant differences were observed in the incidence of acute rejection (p=0.657), although lower incidence of postoperative complications, including acute kidney injuries or culture-proven infections, were observed in the basiliximab induction group. A subgroup analysis of high-risk and preoperative ECMO support groups showed similar results.

Benazzo A, et al. (2021). Outcomes with alemtuzumab induction therapy in lung transplantation: a comprehensive large-scale single-center analysis. Transplant international: official journal of the European Society for Organ Transplantation, 34(12), 2633–2643. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34738249/

- Retrospective 10-year single center analysis from 2008-2019 of LTR receiving alemtuzumab induction followed by low dose maintenance immunosuppression. Freedom from higher-grade ACR at 1, 5, and 10 years was 98%, 96%, and 96%, respectively. Thirty-nine patients (5%) developed clinical AMR. Twenty-one percent of patients developed high-grade CKD. A total of 1488 infections were recorded, with 16% diagnosed within the first 3 months. Sixty-two patients (9%) developed a malignancy during follow-up. Freedom from CLAD at 1, 5, and 10 years was 94%, 72%, and 53%, respectively. Overall survival rates at 1, 5, and 10 years were 85%, 71%, and 61%, respectively.

Henderson C, et al. (2020). Rates of Respiratory Viral Infection in Pediatric Lung Transplant Patients After ATG vs.Basiliximab Induction. Am J Respir Crit Care Med. 201, A5133. Retrieved from: https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2020.201.1_MeetingAbstracts.A5133

- Retrospective single center comparison of respiratory viral infections in pediatric lung transplant recipients receiving antithymocyte globulin or basiliximab induction therapy. There was no difference in infection rate or time to first infection between the groups.

Fitzgerald LJ, et al. (2020). Evaluation of Targeted Basiliximab Induction Therapy in Lung Transplant. J Heart Lung Transplant. 39(4), S323. Retrieved from: https://doi.org/10.1016/j.healun.2020.01.1333

- Retrospective single center analysis of basiliximab used in lung transplant recipients with acute kidney injury. No difference was found in rates of acute rejection or CLAD in those patients that received basiliximab vs those who did not, however more patients in the basiliximab group died at 1 year.

Benazzo A, et al. (2019). Donor-Specific Antibodies and Antibody-Mediated Rejection after Alemtuzumab Induction Therapy: A Retrospective Analysis of a High-Volume Lung Transplant Center. J Heart Lung Transplant. 38(4), S166-S167. Retrieved from: https://www.jhltonline.org/article/S1053-2498(19)30400-0/fulltext

- Retrospective single center analysis of all patients who received alemtuzumab as induction therapy. De novo DSAs developed in 17.7%, AMR diagnosed in 3.8%, and 5-year survival was worse in those who developed AMR.

Li KHC, et al. (2018). Acute Cellular Rejection and Infection Rates in Alemtuzumab vs Traditional Induction Therapy Agents for Lung and Heart Transplantation: A Systematic Review and Meta-analysis. Transplant Proc. 50(10), 3739-3747. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30577263/

- Systematic review and meta-analysis of alemtuzumab in heart or lung transplant recipients. Alemtuzumab was associated with less acute cellular rejection compared to antithymocyte globulin and lower infection and acute rejection rates compared to basiliximab.

Benazzo A, et al (2018). Alemtuzumab induction combined with reduced maintenance immunosuppression is associated with improved outcomes after lung transplantation: A single centre experience. PLoS ONE, 14(1), e0210443. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30645645/

- Retrospective single center analysis including 446 lung transplant recipients, 52% received alemtuzumab, 11% received antithymocyte globulin, and 37% received no induction therapy. The alemtuzumab group had the lowest rate of chronic kidney insufficiency and infection in the first year. Improved survival and low rates of ACR, lymphocytic bronchiolitis, and CLAD were found in the group receiving any induction therapy.

Furuya Y, et al. (2016). The impact of alemtuzumab and basiliximab induction on patient survival and time to bronchiolitis obliterans syndrome in double lung transplantation recipients. Am J Transplant. 2016; 16(8): 2334-41. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/26833657

- Retrospective UNOS Registry study in 6117 lung transplant recipients demonstrating longer median survival for alemtuzumab and basiliximab versus no induction. Recipients of alemtuzumab had a lower incidence of BOS at 5 years.

Whited LK., et al. (2015). Evaluation of alemtuzumab versus basiliximab induction: a retrospective cohort study in lung transplant recipients. Transplantation, 99(10): 2190-5. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/25769073

- Retrospective comparison showed that alemtuzumab was associated with superior outcomes with biopsy score and lower incidence of grade 2 or higher rejection at 6 months but no difference in overall graft or patient survival between the 2 groups.

Sweet SC. (2013). Induction therapy in lung transplantation. Transpl Int. Jul;26(7):696-703. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/23701023/

- Review of agents used for induction in lung transplant and future directions

Penninga L, et al. (2013). Antibody induction therapy for lung transplant recipients. Cochrane Database Systemic Review, 27, 11. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/24282128

- Cochrane review of T-cell antibody induction (ATG, ALG, IL2RA, alemtuzumab, and OKT3) in lung transplant showed no clear benefit or harm of antibody induction compared to no induction or when comparing different types of antibody induction.

Jaksch P, et al. (2013). Antithymocyte globulin induction therapy improves survival in lung transplantation for cystic fibrosis. Transplant International, 26, 31-41. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23145940

- Retrospective analysis of induction strategy in lung transplant recipients with CF at a single center. ATG induction was associated with a survival benefit at 1- 3- and 5-years, lower rates of acute rejection, and no increased rate of infection verses no induction.

Shyu, S, et al. (2011). Five-year outcomes with alemtuzumab induction after lung transplantation. The Journal of Heart and Lung Transplantation, 30, 743-754. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/21420318

- Single-center retrospective comparison showing that alemtuzumab was associated with greater 5-year freedom from ACR, lymphocytic bronchiolitis, OB, and BOS.

Van Loenhout KC, et al. (2010). Early outcomes using alemtuzumab induction in lung transplantation. Interactive Cardiovascular and Thoracic Surgery, 10, 190-4. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/19939852

- Single-center prospective study showing alemtuzumab induction with reduced dose maintenance IS was similar to no induction/standard dose IS in terms of ACR, death, and infection at 6 and 12 months.

Clinckart F, et al. (2009). Basiliximab as an alternative to antithymocyte globulin for early immunosuppression in lung transplantation. Transplant Proceedings, 41, 607-9. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/19328937

- Single-center comparison of basiliximab and ATG showing no difference in ACR or infections in 37 lung transplant recipients.

Hartwig M, et al. (2008). Rabbit anti-thymocyte globulin induction therapy does not prolong survival after lung transplantation. The Journal of Heart and Lung Transplant, 27, 547-53. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/18442722

- Prospective, single-center comparison of RATG and no induction showing no difference in graft survival, overall rejection, and infection, though there was a lower rate of early rejection with RATG.

Hachem R, et al. (2008). The impact of induction on survival after lung transplantation: an analysis of the International society for Heart and Lung Transplantation Registry. Clinical Transplantation, 22, 603-8. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/18435784

- ISHLT registry study of 3970 adult lung transplant recipients suggesting that IL2RA and ATG are each associated with a survival benefit following lung transplant. Those treated with IL2RA had better graft survival than those treated with ATG and those who did not receive induction.

Ailawadi G, et al. (2008). Effects of induction immunosuppression regimen on acute rejection, bronchiolitis obliterans, and survival after lung transplantation. Journal of Thoracic and Cardiovascular Surgery, 135, 594-602. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/18329476

- Single-center retrospective review showing daclizumab was associated with significantly less acute rejection and bronchiolitis obliterans than those receiving ATG with a trend towards improved survival, though confounded by the use of MMF.

Hachem R, et al. (2005). A comparison of basiliximab and anti-thymocyte globulin as induction agents after lung transplantation. The Journal of Heart and Lung Transplantation, 24, 1320-6. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/16143251

- Retrospective comparison showed that ATG associated with lower rate of acute rejection and BOS compared with basiliximab without increasing the risk for CMV.

Borro JM, et al. (2005). Comparative study of basiliximab treatment in lung transplantation. Transplant Proc. Nov;37(9):3996-8. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/16386608/

- Compared incidence of acute and chronic rejection in patients who received basiliximab induction vs those who did not. Acute rejection was 13.3% in basiliximab group vs 38.5% in no induction group (P = 0.19, OR 4.06). Chronic rejection in 20% in the basiliximab group vs 38.5% in no induction group respectively (P = 0.4, OR 2.5). Basiliximab use trended towards less rejection.

Palmer SM, et al. (1999). Rabbit antithymocyte globulin decreases acute rejection after lung transplantation: results of a randomized, prospective study. Chest, 116(1), 127-33. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/10424515

- Prospective, randomized, single-center comparison of RATG (1.5 mg/kg/dose x3 doses) versus no induction therapy + CSA/AZA/Pred; induction was associated with a lower rate of biopsy-proven grade II or greater rejection and a nonsignificant decrease in BOS with similar infection/malignancy occurrences.

6.2. Maintenance therapy

Erdman J, et al. (2022). Lung Transplant Outcomes in Adults in the United States: Retrospective Cohort Study Using Real-world Evidence from the SRTR. Transplantation, 106(6), 1233–1242. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34974456/

- Retrospective review of SRTR data to analyze the efficacy and safety of tacrolimus based IS regimens in adult lung transplant recipients. Risk of graft failure or death was significantly higher in adults receiving CsA + MMF or CsA + AZA compared with TAC + MMF, with no significant difference seen between TAC + MMF and TAC + AZA. TAC + MMF had the highest continued use at 1 y posttransplant (72.0% versus 35.4%-51.5% for the other regimens). There was no increase in the rate of infection or malignancy in the TAC + MMF group.

Scheffert JL, et al. (2014). Immunosuppression in lung transplantation. J Thorac Dis. 2014 Aug;6(8):1039-53. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/25132971/

- Summarizes the use of available induction and maintenance immunosuppressive strategies in lung transplantation.

Snell GI, et al. (2013). Immunosuppression and allograft rejection following lung transplantation: evidence to date. Drugs, 73, 1793-1813. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/24142409

- Summary of currently available immunosuppression strategies including alternative routes of administration (intravenous, sublingual, inhaled) and use of generic immunosuppressants.

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6.2.1 Calcineurin inhibitors

Katada Y, et al. (2022). Association between time in therapeutic range of tacrolimus blood concentration and acute rejection within the first three months after lung transplantation. Journal of pharmaceutical health care and sciences, 8(1), 25. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36180948/

- Retrospective single center study of LTR to evaluate the association between tacrolimus trough levels (goal 10-15 ng/mL) and clinical outcomes. There were no differences in the tacrolimus time in therapeutic range (TTR) between the early-acute rejection group (2 weeks

post transplant) vs no acute rejction. For late acute rejection (AR) (after 1 month post-op), the tacrolimus TTR during postoperative days (POD) 21-30 and POD 31-onset was significantly lower in the late-AR group than the no-AR group (50.0 ± 7.1 vs. 71.8 ± 18.0% and 37.0 ± 26.6 vs. 68.9 ± 31.5%, P<0.05, respectively). The cutoff value of the tacrolimus TTR during POD 21-30 was estimated as 55.0%.

Evans KB, et al. (2022). Impact of Tacrolimus Trough Variability on Acute Rejection Following Lung Transplantation. Transplantation proceedings, S0041-1345(22)00500-0. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36123193/

- Retrospective single center evaluation of tacrolimus level variability with total acute rejection score at 12 months post-transplant. Patients with high tacrolimus variability at 0-3, 3-6, and 6-12 months on average scored 0.18 (mean 1.6 vs 1.5; 95% CI): -0.3 to 0.66, P =.46), 0.14 (mean 1.7 vs 1.5; 95% CI: -0.32 to 0.6, P = .55), and 0.12 (mean 1.6 vs 1.5; 95% CI: -0.34 to 0.58, P = .62) point higher in 12-month total acute rejection scores, respectively; however, these differences were not statistically significant.

Godinas L, et al. (2021). Once daily tacrolimus conversion in lung transplantation: A prospective study on safety and medication adherence. The Journal of heart and lung transplantation: the official publication of the International Society for Heart Transplantation, 40(6), 467–477. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33840608/

- Prospective cohort study (N=372) evaluated lung function, rejection, renal function, metabolic parameters, and adherence in lung transplant recipients converted from tacrolimus twice daily immediate-release to once daily extended-release formulation. Outcomes were evaluated 6 months before and 12 months following conversion. Authors concluded that conversion to tacrolimus once daily extended-release formulation was safe with regards to the outcomes evaluated and an improvement in medication adherence was observed.

Braithwaite HE, et al. (2021). Identifying the association between tacrolimus exposure and toxicity in heart and lung transplant recipients: A systematic review. Transplantation reviews (Orlando, Fla.), 35(2), 100610. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33756310/

- Systematic review to identify correlations between PK measures of tacrolimus exposure in heart and lung recipients and tacrolimus toxicities. Elevated tacrolimus C_0 was associated with AKI occurrence and severity in three observational studies and was a predictor of renal impairment in 6 studies. One study found that for each 5 ng/mL per year of tacrolimus exposure, defined by consecutive AUC, eGFR declined by 1.3 mL/min/1.73m2 ($p < 0.001$). Comparatively, 2 studies failed to find a significant association between nephrotoxicity and tacrolimus exposure. Neurotoxicity occurred both with tacrolimus C_0 within therapeutic range and with supratherapeutic C_0. No significant association was found between NODAT and tacrolimus C_0 in two studies. One study reported on gastrointestinal toxicity, with supratherapeutic C_0 and elevated peak concentration in one lung transplant recipient three days prior to symptom development.

Miano TA, et al. (2020). Early Tacrolimus Concentrations After Lung Transplant Are Predicted by Combined Clinical and Genetic Factors and Associated With Acute Kidney Injury. Clinical Pharmacology and Therapeutics. 107(2):462-470. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31513279/

- Retrospective review of 494 lung transplant recipients within a single center to evaluate effect of clinical and pharmacogenetic predictors of tacrolimus-induced AKI. Overall, 60% of patients developed AKI between post-operative days 4-14. Trough levels greater than 12 ng/mL were most predictive of AKI development, and risk of AKI was predicted to increase 54% for each 5 ng/mL increase in average concentrations. Using concentration:dose ratios (CDR), the effect of various genotypes and clinical factors were evaluated. Greatest positive percent change in CDR was observed in patients with voriconazole exposure (+79.7, 95% CI 65.1 to 95.5) whereas greatest negative percent change in CDR was observed in CYP3A5 extensive metabolizers (-60.7, 95% CI -72.8 to -43.4).

Sintes H, et al. (2018). Pharmacokinetic Study of Conversion Between 2 Formulations of Once-daily Extended-release Tacrolimus in Stable Lung Transplant Patients. Transplantation. Oct;102(10):e439-e446. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29965950/

- Phase II trial evlautating the use of ER tacrolimus once daily (LCPT) vs once daily prolonged-release tacrolimus (ODT) in lung transplantation which determined the transition was safe and tolerated.

Ensor C, et al. (2018). Increasing tacrolimus time in therapeutic range is associated with superior one-year outcomes in lung transplant recipients. Am J Transplant. 18(6), 15271533. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/29513387

- A single-center, observational, cross-sectional study of 292 lung transplant recipients looking at the effects of tacrolimus time-in-therapeutic range (TTR). Increasing TTR by 10% was associated with a significantly lower likelihood of high-burden ACR at 1 year ($P < .001$) and with lower rates of CLAD ($P < .001$) and mortality ($P < .001$) at 1 year.

Calabrese DR, et al. (2018). Genotypes associated with tacrolimus pharmacokinetics impact clinical outcomes in lung transplant recipients. Clin Transplant. 32(8): e13332. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29920787/

- Single center, retrospective cohort study including 321 lung or heart-lung transplant recipients. Single nucleotide polymorphisms (SNPs) for the ABCB1, CYP3A4, and CYPA5 genes were categorized for all patients. Linear models adjusted for subject characteristics. CYP3A intermediate and extensive metabolizers spent less time in goal tacrolimus range compared to poor metabolizers. Patients with high ABCB1 function (carriers of ABCB1 CGC-CGC diplotype) has three times greater odds of developing KDIGO stage II or greater AKI as compared to TTT-TTT diplotype (P=-.01). No differences in time to CLAD or death among ABCB1 genotypes or CYP3A genotypes.

Treede H, et al. (2012). 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. Journal of Heart and Lung Transplantation, 31, 797-804. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22554673

- Prospective, randomized, multicenter, international, open-label investigation of tacrolimus (n = 124) compared to cyclosporine (n = 125) in combination with mycophenolate and prednisone. The primary endpoint of cumulative BOS incidence at three years was significantly lower in the tacrolimus group (P = 0.037). No significant difference in acute rejection or patient survival at one and three years. Incidences of infection were also similar, while development of renal dysfunction was more common in the tacrolimus group (P = 0.09).

Fan Y, et al. (2009). Tacrolimus versus cyclosporine for adult lung transplant recipients: a meta-analysis. Transplant Proc. 41(5), 1821-4. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/19545736/

- Meta-analysis of 297 patients from randomized controlled trials comparing tacrolimus to cyclosporine. Mortality at 1 year or more was comparable between the treatment groups. Tacrolimus-treated patients experience fewer incidences of acute rejection (P=0.04), however they also experienced a higher rate of new-onset diabetes (P=0.003).

Monchaud C, et al. (2009). Pharmacokinetic Optimization of Immunosuppressive Therapy in Thoracic Transplantation: Part I. Clinical Pharmacokinetics, 48, 419-462. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/19691367

- First of a two-part review, detailing the pharmacokinetics and therapeutic drug monitoring for calcineurin inhibitors in thoracic transplantation.

Muhammet CR, et al. (2009). Tacrolimus and azathioprine versus cyclosporine and mycophenolate mofetil after lung transplantation: a retrospective cohort study. Journal of Heart and Lung Transplantation, 28(7), 697-703. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/19560698

- Retrospective review of 120 lung transplant recipients maintained on either cyclosporine and mycophenolate (n = 37) or tacrolimus and azathioprine (n = 83) in combination with prednisone and IL-2 receptor antagonist induction. Patients in the tacrolimus/azathioprine group had significantly better pulmonary function as measured by FEV1 and FVC at 12 months. No differences in acute rejection, BOS or survival were observed.

Hachem RR, et al. (2007). A randomized controlled trial of tacrolimus versus cyclosporine after lung transplantation. Journal of Heart and Lung Transplantation, 26, 1012-1018. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/17919621

- Prospective, randomized study comparing tacrolimus (n = 44) and cyclosporine (n = 46) in combination with azathioprine and prednisone. The primary endpoint (composite of cumulative acute rejection, lymphocytic bronchitis or BOS) occurred more in the cyclosporine group (P = 0.002). Cumulative acute rejection or lymphocytic bronchitis was also significantly less in the tacrolimus group and BOS stages 0-p and 1 trended towards higher incidence in the cyclosporine group. The incidence of CMV and community-acquired respiratory viruses was greater in the cyclosporine group; bacterial, fungal and total infections were similar.

Wang J, et al. (2006). Impact of ABCB1 (MDR1) haplotypes on tacrolimus dosing in adult lung transplant patients who are CYP3A5 *3/*3 non-expressors. Transpl Immunol. Jan;15(3):235-40. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/16431292/

- Evaluated influence of ABCB1 polymorphisms on tacrolimus dosing in CYP3A5 *3/*3 non-expressors. Three polymorphism of ABCB1 were noted: CGC, TTT, and CGT. Tacrolimus levels and doses were lower in patients with GCG and TTT specific ABCB1 polymorphisms.

Zuckermann A, et al (2003). Cyclosporine A versus tacrolimus in combination with mycophenolate mofetil and steroids as primary immunosuppression after lung transplantation: One-year results of a 2-center prospective randomized trial. Journal of Thoracic and Cardiovascular Surgery, 125,891-900. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/12698153

- Prospective, randomized, two-center investigation comparing tacrolimus (n = 37) and cyclosporine (n = 37) in combination with mycophenolate, prednisone and ATG induction.

No significant differences in number of treated rejection episodes, freedom from acute rejection and BOS, or survival at 6 and 12 months were observed.

Treede H, et al. (2001). Tacrolimus versus Cyclosporine after Lung Transplantation: A Prospective, Open, Randomized Two-Center Trial Comparing Two Different Immunosuppressive Protocols. Journal of Heart and Lung Transplantation, 20, 511-517. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/11343977

- Prospective, randomized comparison of tacrolimus (n = 26) and cyclosporine (n = 24) in combination with mycophenolate, prednisone and rATG induction. The tacrolimus group had significantly fewer treated rejection episodes and rejection-free survival at 6 and 12 months was numerically greater for the tacrolimus group. Six and 12-month survival and incidences of infection were similar. Serum creatinine did not differ significantly between the groups. Cyclosporine-treated patients experienced more hypertension and hyperlipidemia requiring treatment, whereas as NODAT was only observed in the tacrolimus group.

Keenan RJ, et al. (1995). Clinical trial of tacrolimus versus cyclosporine in lung transplantation. Annals of Thoracic Surgery, 60, 580-585. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/7545889

- Prospective, randomized study comparing tacrolimus (n = 66) and cyclosporine (n = 67) in combination with azathioprine and prednisone. Patients receiving tacrolimus experienced fewer acute rejection episodes per 100 patient days (P = 0.07) as well as significantly less BOS. The total incidence of infection was similar. However, bacterial pneumonia was more common the cyclosporine group and fungal infections were more common in the tacrolimus group. No differences in one and two-year survival were observed.

6.2.2 Cell cycle inhibitors

Steinack C, et al. (2022). Influence of mycophenolate mofetil dosage and plasma levels on the occurrence of chronic lung allograft dysfunction in lung transplants: a retrospective cohort analysis. Swiss medical weekly, 152, w30206. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35964254/

- Retrospective cohort study of 71 LTR that evaluated whether the dose of the immunosuppressant mycophenolate mofetil or plasma concentrations of the active metabolite mycophenolic acid affect the development of CLAD. 37 patients did not develop CLAD and 34 patients developed CLAD. Mean mycophenolic acid did not differ significantly between the groups. In the first 4 post-transplant years the death rate was 25%. A total of 50% of the patients died by the ninth post-transplant year. There was a dose-effect relationship between mycophenolate mofetil dosage, mycophenolic acid ($r2 = 0.02$, $p < 0.001$), as well as lymphocyte levels ($r2 = -0.007$, $p < 0.001$), but only the traditional risk factor of age predicted CLAD. Continuously measured mycophenolic acid did not predict chronic lung allograft dysfunction (hazard ratio 0.98, 95% confidence interval 0.90-1.06, $p = 0.64$ over a period of 382.97 patient-years).

Joerns J, et al. (2022). High-dose Mycophenolate Use at Vaccination Is Independently Associated With Breakthrough COVID-19 Among Lung Transplant Patients. Transplantation, 106(5), e271–e274. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35250007/

- Single-center retrospective chart review study comparing a cohort of LTR vaccinated for COVID-19 with breakthrough infection to a control group of vaccinated LTR who did not develop COVID-19 during the 6 months following vaccination. LTR with breakthrough infection were more likely to be on MMF as the antimetabolite (P = 0.15), and a higher proportion of patients with breakthrough infection were on daily MMF dose of >1000 mg

(P = 0.03). When compared with azathioprine or MMF dose of ≤1000 mg/d, the risk of breakthrough infection was significantly higher among patients on a daily MMF dose of >1000 mg (P = 0.006).

Yabuki H, et al. (2020). Plasma mycophenolic acid concentration and the clinical outcome after lung transplantation. Clinical Transplantation. 00; e14088. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32949050/

- Cohort study of mycophenolic acid (MPA) AUC0-12 between groups stratified based on outcomes including no events, infection, and CLAD. MPA AUC0-12 was significantly higher in the infection group and significantly lower in the CLAD group. Thresholds for these outcomes were established at 22 to 40 µg·h/mL for avoidance of infection and CLAD, respectively.

Tague K, et al. (2020). Impact on SLCO1B3 Polymorphisms on Clinical Outcomes in Lung Allograft Recipients Receiving Mycophenolic Acid. The Pharmacogenomics Journal. 20.1: 69-79. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30992538/

- Retrospective cohort study that analyzed effect of known single nucleotide polymorphisms on outcomes such as survival, ≥ A2 or B2 acute rejections, and CLAD. SLCO1B3 SNPs rs 4149117 and rs7311358 were associated with decreased 1 and 3-year survival, rejection, and shorter survival following CLAD diagnosis.

Vos M, et al. (2018). Azathioprine to mycophenolate mofetil transition and risk of squamous cell carcinoma after lung transplantation. The Journal of Heart and Lung Transplantation, 37(7), p853–85. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/29680587

- A review of data of 544 patients from the Dutch nationwide registry of histopathology (PALGA) looking at the incidence of squamous cell carcinoma (SCC) and associated risk factors. Sequential use of azathioprine and mycophenolate mofetil was associated with a lower risk of SCC compared with azathioprine use only.

Speich R, et al (2010). Mycophenolate mofetil reduces alveolar inflammation, acute rejection and graft loss due to bronchiolitis obliterans syndrome after lung transplantation. Pulmonary Pharmacology and Therapeutics, 23, 445-449. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/20394831

- Prospectively collected data from 176 consecutive lung transplant recipients was compared to evaluate the use azathioprine and mycophenolate in combination with cyclosporine and prednisone. Patients in the mycophenolate group experienced fewer acute rejection episodes as well as decreased severity of rejection compared to azathioprine. Despite similar incidences of BOS, the mycophenolate group had significantly less graft loss due to BOS.

Monchaud C, et al. (2009). Pharmacokinetic optimization of immunosuppressive therapy in thoracic transplantation: part II. Clinical Pharmacokinetics, 48, 489-516.
Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/19705921

- Second component of comprehensive review, including pharmacokinetics and therapeutic drug monitoring for mycophenolate and mTOR inhibitors.

McNeil K, et al. (2006). Comparison of mycophenolate mofetil and azathioprine for prevention of bronchiolitis obliterans syndrome in de novo lung transplant recipients. Transplantation, 81, 998-1003. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/16612275

- Prospective, randomized, international, multicenter, open-label study comparing azathioprine and mycophenolate in combination with cyclosporine, prednisone and ATG induction. No difference in the incidence of acute rejection at one or three years or time to acute rejection was observed. Additionally, no differences in incidence, severity, time to development of BOS or survival were detected at three years.

Palmer SM, et al. (2001). Results of a randomized, prospective, multicenter trial of mycophenolate mofetil versus azathioprine in the prevention of acute lung allograft rejection. Transplantation. Jun 27;71(12):1772-6. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/11455257/

- Randomized, prospective, open-lable multicenter trial evaluated use of mycophenolate vs azathioprine in lung transplantation. Study suggests a trend towards better rejection rate and overall survival at 6 months with mycophenolate, but this is not statistically significant.

6.2.3 Mammalian target of rapamycin inhibitors

Schmucki K, et al. (2023). Mammalian Target of Rapamycin Inhibitors and Kidney Function After Thoracic Transplantation: A Systematic Review and Recommendations for Management of Lung Transplant Recipients. Transplantation, 107(1), 53–73. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36508646/

- Systematic review that examined the efficacy and safety of mTOR inhibitors after lung transplantation as well as their effect on kidney function. Clinical considerations for mTOR inhibitor use are described by the authors.

Ivulich S, et al. (2023). Everolimus Based Immunosuppression Strategies in Adult Lung Transplant Recipients: Calcineurin Inhibitor Minimization Versus Calcineurin Inhibitor Elimination. Transplant international: official journal of the European Society for Organ Transplantation, 36, 10704. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36744051/

- Retrospective single-center study of 217 LTRs who were initiated on everolimus (EVE). 120 of these were with a CNI minimization regimen and 97 with CNI elimination. Survival outcomes were calculated on the date of EVE commencement. On multivariate analysis, the CNI elimination strategy had poorer survival outcomes compared to the CNI minimization strategy [HR 1.61, 95% CI: 1.11–2.32, p=0.010]. Overall survival at 1, 3, and 5 years favored the CNI minimization strategy. Utilization of EVE for renal preservation was associated with improved survival compared to other indications [HR 0.64, 95% CI: 0.42–0.97, p=0.032]. No statistically significant difference was seen between groups for ACR and CLAD outcomes.

Turkkan S, et al. (2022). Everolimus Use in Lung Transplant Recipients. Transplantation proceedings, S0041-1345(22)00569-3. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36192210/

- Retrospective observational study investigating everolimus switch for: CLAD, kidney impairment, and malignant neoplasm groups. The number of ACR, CMV, and aspergillosis infection cases before switch were 7, 13, and 2, respectively, and 7, 2, and 3 after. Renal function of the whole population after the switch improved, but difference was onlysignificant in tacrolimus nephrotoxicity group. Three of 5 patients in the CLAD group remained stable after switching. Only 1 of 7 patients with malignant neoplasms had a recurrence during 31.1 (16.5) months of median follow-up. Eleven cases of everolimus adverse effects occurred in 9 patients (47.3%), with 2 (10.5%) withdrawal events.

Kneidinger N, et al. (2022). Five-year Outcome of an Early Everolimus-based Quadruple Immunosuppression in Lung Transplant Recipients: Follow-up of the 4EVERLUNG Study. Transplantation, 106(9), 1867–1874. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35283454/

- An investigator-initiated 5-y follow-up analysis of the 4EVERLUNG study (NCT01404325), comparing everolimus-based quadruple low CNI with standard triple regimen. 123 patients (95%) from the core study were analyzed. During the observation period in 11 patients (19%) of the standard triple regimen and in 30 patients (46%) of the quadruple low CNI regimen, the assigned immunosuppressive regimen was switched (P = 0.002). eGFR at 5-y follow-up did not differ between the groups. Thromboembolic events occurred more frequently in the quadruple low CNI regimen (ITT: 11% versus 24%, P=0.048; PP: 11% versus 22%, P=0.162). There was a trend for a higher CLAD-free survival for the quadruple low CNI regimen in the PP population (P=0.082). No difference in the graft survival was found.

de Souza AR, et al. (2021). Mammalian Target of Rapamycin Inhibitors Vs Calcineurin Inhibitors in Chronic Graft Rejection After Lung Transplantation: A Systematic Review and Meta-Analysis. Transplantation proceedings, 53(10), 3056–3064. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34785027/

- Systematic review of three RCTs (SHITRIT, NOCTET, and 4EVERLUNG) comparingmTOR inhibitor immunosuppression associated with low-dose calcineurin inhibitors with isolated calcineurin inhibitor immunosuppression on the new-onset chronic rejection development and mortality 12 months after lung transplantation. There was an increase in the number of adverse events (P = .0064) and improved renal function (P < .0001) with mTOR inhibitor-based regimens. The other outcomes indicated a trend toward greater risk of death and acute graft rejection with the use of mTORs.

Wijesinha M, et al. (2019) Survival Associated with Sirolimus plus Tacrolimus Maintenance Without Induction Therapy Compared with Standard Immunosuppression After Lung Transplant. JAMA Netw Open, 2(8): E1910297. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31461151/

- Retrospective cohort study of 9,019 lung transplant recipients who received either sirolimus plus tacrolimus or tacrolimus plus mycophenolate mofetil. The primary outcome was survival. A survival benefit was seen in patients receiving sirolimus plus tacrolimus without induction therapy when compared to mycophenolate mofetil plus tacrolimus with induction therapy (median survival 10.7 years, HR 0.48, 95% CI 0.31-0.76).

Gottlieb J, et al (2019). A randomized trial of everolimus-based quadruple therapy vs standard triple therapy early after lung transplantation. Am J Transplant. 19(6):1759-1769. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30615259/

- Prospective, randomized, open label 12-month multicenter trial including lung transplant patients 3-8 months following transplant aimed at evaluating impact of low-CNI exposure regimens in patients with baseline renal dysfunction. Patients were stratified based on eGFR before randomization. The primary endpoint was eGFR after 12 months. Patients receiving quadruple low CNI regimens had superior renal function compared to the standard triple therapy group (64.5 ml/min vs 54.6 ml/min, p <0.001). BPAR, CLAD and death were similar between two groups.

Wojarski J, et al (2018). Early Sirolimus-Based Immunosuppression is Safe for Lung Transplantation Patients: Retrospective, Single Arm, Exploratory Study. Ann Transplant. 23;23:598-607. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30135417/

- A retrospective, single arm, exploratory study of groups of patients evaluating safety of using sirolimus early post-operatively. Early sirolimus administration was defined as administration within first 30 days post-transplantation. Thirteen patients received early sirolimus based immunosuppression along with cyclosporine and prednisone, as well as induction therapy. Thirty-day mortality was 0% and no anastomotic dehiscence was observed, even with administration as early as POD15. Four patients experienced sever acute cellular rejection within the first year following transplant. One patient developed bronchiolitis obliterans syndrome.

Streuber M, et al. (2016). Everolimus versus mycophenolate mofetil de novo after lung transplantation: A prospective, randomized, open-label trial. Am J Transplant.; 16(11), 3171-3180. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27104933

- Randomized control trial in 190 lung transplant recipients assigned to either cyclosporine, prednisone, mycophenolate or cyclosporine, prednisone, everolimus 28 days after transplant. BOS-free survival was similar via the intention-to-treat analysis at two years. The per-protocol analysis demonstrated less incidence of BOS in the everolimus arm with less CMV infection, ACR, and lower respiratory infections, despite a more pronounced dropout rate.

Glanville AR, et al (2015). Three-year results of an investigator-driven multicenter, international, randomized open-label de novo trial to prevent BOS after lung transplantation. The Journal of Heart and Lung Transplantation. 34(1), 16-25. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/25049068

- A multicenter, prospective, international, randomized open-label study of de novo enteric coated mycophenolate sodium (MPS) versus delayed-onset everolimus (RAD) in combination with cyclosporine and corticosteroids. Three-year ITT analysis found no significant difference between treatment arms in freedom from BOS but was underpowered to accept the null hypothesis that RAD and MPS have equivalent efficacy in preventing BOS, or death after lung transplantation.

Schneer S, et al. (2014). Renal function preservation with the mTOR inhibitor, Everolimus, after lung transplant. Clinical Transplantation, 28(6):662-8. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/24738962

- Retrospective review of 41 lung transplant recipients who were treated with everolimus and lower dose calcineurin inhibitors. Renal function preservation was greater when everolimus was initiated before CrCl deterioration or proteinuria development.

Sacher VY, et al. (2014). Effects of prophylactic use of sirolimus on bronchiolitis obliterans syndrome development in lung transplant recipients. Annals of Thoracic Surgery, 97(1):268-74. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/24119986

- Twenty-four lung transplant recipients who were converted to an immunosuppression regimen consisting of tacrolimus, sirolimus and prednisone were compared to those on a regimen of tacrolimus, mycophenolate or azathioprine and prednisone. The sirolimus group was found to have a lower incidence of BOS and viral infections and improved survival.

De Pablo A, et al. (2013). Recommendations on the use of everolimus in lung transplantation. Transplantation Reviews, 27, 9-16. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23276646

- Consensus document generated by experts representing Spanish lung transplant centers that summarizes everolimus pharmacokinetics, therapeutic drug monitoring and potential indications for use in lung transplantation.

Roman A, et al. (2011). A retrospective 12-month study of conversion to everolimus in lung transplant recipients. Transplant Proc. Sep;43(7):2693-8. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/21911148/

- Retrospective study evaluated 12-month outcomes of everolimus in lung transplant recipients. Showed that bronchiolitis obliterans syndrome and renal insufficiency were main reason for transitions, renal function improved overtime with transition.

Bhorade S, et al (2011). Comparison of sirolimus with azathioprine in a tacrolimus-based immunosuppressive regimen in lung transplantation. American Journal of Respiratory and Critical Care Medicine, 183, 379-387. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/20833822

- Report of a prospective, multicenter, randomized, controlled trial comparing azathioprine to sirolimus initiated at least three months post-transplant in combination with tacrolimus, prednisone and IL-2 receptor antagonist induction (n = 181). No differences in acute rejection, development of bronchiolitis obliterans syndrome (BOS) or survival at 12 and 36 months were observed. Significantly more patients in the azathioprine group experienced CMV infection, while significantly more in the sirolimus groups experienced significant adverse events and early discontinuation.

Snell GI, et al. (2006). Everolimus versus Azathioprine in Maintenance Lung Transplant Recipients: An International, Randomized, Double-Blind Clinical Trial. American Journal of Transplantation, 6, 169-177. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/16433771

- Prospective, randomized, international, multicenter, double-blind investigation comparing azathioprine (n = 112) to everolimus (n = 101) in combination with cyclosporine and prednisone. Everolimus was uniformly dosed 1.5 mg twice a day and not adjusted based on trough concentrations (median 6.6 ng/mL, 10th to 90th percentile: 2.8-11.8 ng/mL). The everolimus group experienced significantly less efficacy failure (composite endpoint including decline in FEV1 > 15%, graft loss, death or loss to follow up) as well as decline in FEV1 associated with BOS and acute rejection at 12 months. Elevated serum creatinine and discontinuation due to adverse events were more common in the everolimus group.

Shitrit D, et al. (2005). Use of sirolimus and low-dose calcineurin inhibitor in lung transplant recipients with renal impairment: results of a controlled pilot study. Kidney Int. Apr;67(4):1471-5. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/15780099/

- Patients were placed into groups to receive standard immunosuppression vs sirolimus + low dose calcineurin inhibitor. A significant improvement in renal function was seen in the sirolimus group (42.6 mL/min vs. 32.5 mL/min, P= 0.05).

Groetzner J, et al. (2004). Airway anastomosis complications in de novo lung transplantation with sirolimus-based immunosuppression. Journal of Heart and Lung Transplantation, 23, 632-638. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/15135383

- Pilot study reporting bronchial anastomotic complications in three of four lung transplant recipients maintained on sirolimus, tacrolimus and prednisone immediately posttransplant. The average sirolimus trough concentration was 6.2 ± 1.2 ng/mL. Airway dehiscence developed in two patients, resulting in fatality for one patient. Although within the target range (4-10 ng/mL), the heart-lung transplant recipient had the lowest sirolimus trough concentrations and was the only subject that did not experience wound healing complications.

King-Biggs MB, et al. (2003). Airway anastomotic dehiscence associated with use of sirolimus immediately after lung transplantation. Transplantation, 75, 1437-1443. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/12792493

- Open-label, pilot investigation of 15 consecutive lung transplants receiving sirolimus in combination with tacrolimus and prednisone immediately post-transplant. Sirolimus trough concentrations were highly variable in the first week post-transplant, but, average levels were within or below the target range of 10-15 ng/mL and did not differ among those with and without dehiscence. Four patients experienced airway anastomotic dehiscence; three did not survive. When compared to historical controls, the sirolimus group had significantly worse survival.

6.2.4 Belatacept

Nachiappan A, et al. (2022). Severe Acute Cellular Rejection With High-Grade Lymphocytic Bronchiolitis Following Transition from Tacrolimus to Belatacept in a Lung Transplantation Recipient: A Case Report. Transplantation proceedings, 54(1), 165–168. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34756649/

- Case report of a 53-year-old LTR who developed progressive chronic kidney disease related to tacrolimus 3 years post-transplant. He was transitioned off tacrolimus to belatacept to prevent the need for dialysis. He was admitted 2 months later with acute hypoxemic respiratory failure. Video-assisted thoracic surgery biopsy showed acute fibrinous and organizing pneumonia and A4B2 rejection. He subsequently developed chronic lung allograft dysfunction.

Huang HJ, et al. (2022). A pilot randomized controlled trial of de novo belatacept-based immunosuppression following anti-thymocyte globulin induction in lung transplantation. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons, 22(7), 1884–1892. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35286760/

Two-center pilot randomized controlled trial of de novo immunosuppression with belatacept after lung transplantation to assess the feasibility of conducting a pivotal trial. All participants were treated with rabbit anti-thymocyte globulin for induction immunosuppression. Randomization and treatment with belatacept was permanently stopped after three participants in the Belatacept arm (n=13) died compared to none in the Control arm (n=14). Subsequently, two additional participants in the belatacept arm died for a total of five deaths compared to none in the Control arm (p = .016). Asignificant difference was not detected in DSA development, acute cellular rejection, or infection between the two groups.

Iasella CJ, et al. (2018). Maintenance belatacept-based immunosuppression in lung transplantation recipients who failed calcineurin inhibitors. Transplantation. 102(1): 171-177. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/28691954/

- Single center, retrospective case series including 11 adult lung transplant recipients before and after conversion to belatacept from a calcineurin inhibitor (CNI). Mean follow up was 246 days. There was no difference in acute cellular rejection, infections, or mean arterial pressure. Estimated glomerular filtration rate was significantly higher after converting to belatacept. Progression of chronic lung allograft dysfunction occurred in 2 patients.

Brugiere O, et al. (2018). Fulminant acute respiratory distress syndrome after calcineurin inhibitor-belatacept conversion in a lung transplant recipient. Transplantation. 102(6): e255-256. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29509571/

- Case report of fatal acute respiratory distress syndrome in a single lung transplant recipient at 27 days after converting to belatacept from tacrolimus. The patient was stable prior to the conversion with no history of rejection or antibodies. Due to lack of involvement of the native lung, this manifestation was presumed to be due to rejection.

Timofte I, et al. (2016). Belatacept for renal rescue in lung transplant patients. Transplant International, (4):453-63. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/26678245

- Retrospective review of 8 patients with acute renal failure or refractory renal insufficiency who were initiated on belatacept therapy to reduce calcineurin inhibitor exposure. Glomerular filtration rate remained stable in 2 patients and increased in 5 and there was 1 patient death due to multisystem organ failure.

6.3 Desensitization Therapy

Courtwright A, et al. (2023). The Highly Sensitized Recipient: Pretransplant and Posttransplant Considerations. *Clin Chest Med*. 2023;44(1):85-93. Retrieved from: https://pubmed-ncbi-nlm-nih-gov.treadwell.idm.oclc.org/36774171/

- In this review, the authors discuss strategies for improving access to transplant in this population, including risk stratification of crossing pretransplant donor-specific antibodies, based on antibody characteristics. The authors also review institutional protocols, such as perioperative desensitization, for tailoring transplant immunosuppression in the highly sensitized population. The authors conclude with suggestions for future research, including development of novel donor-specific antibody–directed therapeutics.

Roux A, et al. (2022). First use of imlifidase desensitization in a highly sensitized lung transplant candidate: a case report [published online ahead of print, 2022 Dec 29]. Am J Transplant. 2022. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36695676/

- This is the first case, to our knowledge, of imlifidase use facilitating transplant in a lung transplant recipient by rapidly depleting all IgG antibodies and removing any preformed DSAs. This approach provides an option for patients who have failed or are unsuitable for previously described desensitization strategies involving anti-thymocyte globulin or anti-CD20 therapy. Furthermore, because the effect of imlifidase is transient, it may offer benefits for subsequent infection risk compared to anti-thymocyte globulin, which renders the patient profoundly immunosuppressed for several months.

Issitt, R, et al. (2022). Lung transplantation in an 18-month-old with donor specific antibodies - The use of intraoperative, targeted plasma exchange. Perfusion, 2676591221114958. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35840547/

- Case report of pediatric primary lung transplant treated with intraoperative target plasma exchange in the setting of late identification of DSAs in the setting of late identification of

DSAs to minimize the risk of hyperacute rejection. From a pre-transplant mean fluorescence intensity of 5002, donor-specific antibodies were undetectable following plasma exchange on single antigen bead assay. Within the first 2 months post-transplant, the patient developed CMV, EBV, and streptococcus viridans infections. At the point of CMV infection, it was noted that the patient had developed de novo DSA antibodies to the DQ2 (MFI 1805) and DR7 antigens (MFI 2218). It is believed that the infections were the triggering event for DSA production.

Young KA, et al. (2021). Lung Transplantation and the Era of the Sensitized Patient. Front Immunol. May 26;12:689420. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34122454/

- Review discusses issues surrounding sensitized lung transplant patients and management strategies.

Aversa M, et al. (2021). Long-term outcomes of sensitized lung transplant recipients after peri-operative desensitization. American journal of transplantation, 21(10), 3444–3448. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34058795/

- Retrospective review of the peri-operative desensitization regimen of plasma exchange, immune globulin, and antithymocyte globulin on DSA positive lung transplants from 2008-2011 (n=340). Among DSA-positive, PRA-positive/DSA-negative, and unsensitized patients, the median allograft survival was 8.4, 7.9, and 5.8 years, respectively (p = .5908), and the median CLAD-free survival was 6.8, 7.3, and 5.7 years, respectively (p = .5448).

Li HJ, et al. (2020). Successful desensitization by post-centrifugal plasma filtration in two highly sensitized heart and lung transplant recipients. Ann Lab Med. 40(5):431-434. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32311860/

- Two patient case series of successful desensitization using post-centrifugal plasma filtration in two heart and lung transplant recipients with multiple DSAs. This is the first report of using PCPF in cardiothoracic transplant recipients. Patients described in this series also received rituximab and/or bortezomib.

Tinckam KJ, et al. (2015). Survival in sensitized lung transplant recipients with perioperative desensitization. American Journal of Transplantation, 15: 417-426.
Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/25612494

- This study evaluated a desensitization protocol (perioperative plasma exchange with or without the use of antithymocyte globulin or immune globulin) in sensitized lung transplant recipients in comparison to standard immunosuppression in unsensitized patients. Thirty-day survival and one-year graft survival were similar. Similar outcomes were seen between DSA-positive, PRA-positive/DSA-negative, and unsensitized patients.

Snyder L, et al. (2014). Antibody desensitization therapy in highly sensitized lung transplant candidates. American Journal of Transplantation, 14: 849-856. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/24666831

- This retrospective study analyzed the efficacy of using a multi-modal desensitization therapy prior to lung transplantation in 18 candidates with cPRA ≥ 80%. Desensitization regimen included plasmapheresis, methylprednisolone, bortezomib, rituximab, followed by intravenous immunoglobulin. In 9 candidates who received a transplant, post-transplant survival was comparable to recipients with pretransplant HLA antibodies who did not undergo the desensitization protocol.

Hayes D, et al. (2013). Human leukocyte antigen sensitization in lung transplant candidates supported by extracorporeal membrane oxygenation. American Journal of Respiratory and Critical Care Medicine, 188(5), 627-8. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23992596

- Case report on two patients describing the impact of ECMO on PRA levels and the need of monitoring for anti-HLA sensitization while on ECMO

Martinu T, et al. (2009). Acute rejection and humoral sensitization in lung transplant recipients. Proceedings of the American Thoracic Society, 6(1), 54-65. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/19131531

- An overview of acute lung allograft rejection, including clinical presentation, diagnosis, histopathologic features, and mechanisms of cellular and humoral rejection. It describes the clinical relevance for presence of HLA antibody and its association with humoral rejection.

Appel JZ, et al. (2005). Utility of peri-transplant and rescue intravenous immunoglobulin and extracorporeal immunoadsorption in lung transplant recipients sensitized to HLA antigens. Human Immunology, 66 (4):378-386. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/15866701

- Retrospective analysis evaluating clinical impact of desensitization therapy with immune globulin and extracorporeal immunoadsorption in sensitized lung transplant recipients

Lau CL, et al. (2000). Influence of panel-reactive antibodies on posttransplant outcomes in lung transplant recipients. The Annals of Thoracic Surgery, 69 (50): 1520-1524. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/10881834

- Retrospective review of clinical outcomes of a single center in sensitized (n= 18) and non-sensitized lung transplant recipients. No difference in acute rejection was observed, however there was an increased incidence of BOS in untreated sensitized recipients vs. unsensitized.

6.4 Management of rejection

Beeckmans H, et al. (2023). Acute Rejection and Chronic Lung Allograft Dysfunction: Obstructive and Restrictive Allograft Dysfunction. Clin Chest Med. 2023;44(1):137-157. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36774160/

- This review discusses current knowledge, barriers, and gaps in acute cellular rejection and chronic lung allograft dysfunction—the greatest impediment to long-term post-transplant survival.

Zaffiri L. (2021). Desensitization and management of allograft rejection. Curr Opin Organ Transplant. 2021 Jun 1;26(3):314-320. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33938468/

- Review summarized current data on desensitization, ACR, AMR, and CLAD.

Parulekar A, et al. (2019). Detection, classification, and management of rejection after lung transplantation. J Thorac Dis. 11(Suppl14):S1732-S1739. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31632750/

- Review article on diagnosis, staging, clinical presentation, and treatment strategies for acute rejection, AMR, and CLAD

6.4.1 Acute cellular rejection

Yeo HJ, et al. (2023). Pre-Existing Non-Human Leukocyte Antigen Antibodies Are Associated with Allograft Rejection after Thoracic Transplantation. Transplant immunology 77 (2023): 101794–101794. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36702359/

- Of 64 patients, 27 (42.2%) patients underwent rejection, with 26 (40.6%) acute cellular rejection and one (1.6%) acute antibody-mediated rejection. Among 33 identified different non-HLA antibodies, only the anti-glutathione S-transferase theta-1 (GSTT1) antibody positive rate was significantly higher in patients with acute rejection compared to those without rejection (14.8% vs. 0%, p = 0.016). The angiotensin II type I receptor positive rate was not significantly different between the two groups (40% vs. 18.5%, p = 0.129). Patients with antibodies against GSTT1 before heart or lung transplantation have an increased risk of acute rejection.

Ju C, et al. (2023). Application of plasma donor-derived cell free DNA for lung allograft rejection diagnosis in lung transplant recipients. BMC Pulm Med. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36703125/

- One hundred and seventy LTRs were enrolled at the First Affiliated Hospital of Guangzhou Medical University between 1 June 2015 and 30 March 2021. Kruskal–Wallis test showed that there were some significant differences in the level of dd-cfDNA (%) among the 4 groups, with $p < 0.001$. Among them, the level of dd-cfDNA (%) was highest (median 2.17, IQR [1.40–3.82]) in AR group, and higher in CLAD group (median 1.07, IQR [0.98–1.31]), but lower in infection group (median 0.71, IQR [0.57– 1.07]) and lowest in stable group (median 0.71, IQR [0.61–0.84]). Plasma dd-cfDNA could be a useful tool for the assessment of lung allograft rejection, including AR and CLAD, and holds promise as a noninvasive biomarker for “allograft injury” in both acute and chronic rejection following lung transplantation.

Subramani MV, et al. (2022). Acute rejection and post lung transplant surveillance. Indian J Thorac Cardiovasc Surg. Jul;38(Suppl 2):271-279. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35340687/

- Review summarizes the current evidence on the evaluation and treatment of acute rejection after lung transplantation.

Renaud-Picard B, et al. (2021). Acute Rejection in the Modern Lung Transplant Era. Semin Respir Crit Care Med. Jun;42(3):411-427. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34030203/

- Review summarizes the most recent evidence on the mechanisms, risk factors, diagnosis, treatment, and prognosis of ACR.

McPheeters C, et al. (2021). Calcineurin Inhibitor-Based Maintenance Immunosuppression in Lung Transplant Recipients: Optimal Serum Levels for Managing Acute Rejection and Renal Function. Transplantation proceedings, 53(6), 1998–2003. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34253383/

- Retrospective, single-center study that reviewed tacrolimus whole blood trough levels (BTLs), grades of acute cellular rejection (ACR), acute rejection scores, and creatinine clearance (CrCl) obtained in LTR within the first year after their transplant procedure. Maintaining tacrolimus >10µg/L did not result in superior control of acute rejection responses but was associated with declining renal function in the first 90 days post-transplant.

Yousef I, et al. (2020). Efficacy of corticosteroids in the treatment of acute cellular rejection in lung transplant patients. Am J Respir Crit Care Med. 201, A5124. Retrieved from:

https://www.atsjournals.org/doi/pdf/10.1164/ajrccm-conference.2020.201.1_MeetingAbstracts.A5124

- Retrospective single center cohort study including lung transplant recipients experiencing ACR. A1 rejection was treated with pulse prednisone or methylprednisolone 1 g depending on clinical presentation, A2 rejection was treated with methylprednisolone 1 g for 3 days followed by prednisone taper. 78.57% had resolution demonstrated by biopsy and 92.52% had symptomatic improvement, though no difference was noted in FEV1.

Munker D, et al. (2020). Safety and efficacy of steroid pulse therapy for acute loss of FEV1 in lung transplant recipients after exclusion of acute cellular rejection. Transplantation Proceedings. 52(1), 309-314. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31926742/

- Retrospective single center cohort study that studied the efficacy and safety of pulse steroids in the absence of ACR as a treatment for a drop in FEV1 of $\geq$ 10%. A minority of patients (mostly those with BAL eosinophilia) responded to pulse steroid regimen of 500 mg IV methylprednisolone on day 1 followed by two doses of 100 mg IV methylprednisolone over the next two days. Severe complications associated with steroids occurred in 12% of patients.

Levy L, et al. (2019). The impact of first untreated subclinical minimal acute rejection on risk for chronic lung allograft dysfunction or death after lung transplantation. Am J Transplant. 20(1): 241-249. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31397939/

- Single center cohort study of 962 untreated spirometrically stable A1 rejection among consecutive lung transplant recipients. Compared to no ACR, there was no significant difference in risk of CLAD or death in the untreated A1 rejection group.

Swarup R, et al. (2011). Timing of basiliximab induction and development of acute rejection in lung transplant patients. The Journal of Heart and Lung Transplantation, 30, 1228-35. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/21764603

- Basiliximab administration prior to implantation of lung compared to administration immediately post-transplant was associated with a lower incidence of acute rejection, yet no differences in survival or bronchiolitis obliterans syndrome.

Palmer S, et al. (1999). Rabbit antithymocyte globulin decreases acute rejection after lung transplantation: Results of a randomized, prospective study. Chest, 116, 127-133. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/10424515

- Single-center study of 44 lung transplant recipients that investigated the impact of rabbit antithymocyte induction on the incidence of acute allograft rejection after lung transplant. There was a significant reduction in biopsy proven rejection with RATG induction vs. no induction with no observed difference in infections and malignancies.

Yousem S, et al. (1996). Significance of clinically silent untreated mild acute cellular rejection in lung allograft recipients. Human Pathology, 27, 269-273. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/8600042

- An analysis of outcomes of 16 untreated lung transplant patients with asymptomatic mild acute cellular rejection. Half of the patients with worsening function without intervention developed BOS relative to those in the spontaneously regressing group.

6.4.2 Antibody mediated rejection

Halverson LP, et al. (2023). Antibody-Mediated Rejection: Diagnosis and Treatment. Clin Chest Med. 2023;44(1):95-103. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36774172/

- In this review, we provide a brief overview of our current understanding of its pathophysiology with an emphasis on donor-specific antibodies before moving on to focus on the current diagnostic criteria and treatment strategies. Our goal is to discuss the limitations of our current knowledge and explore how novel diagnostic and therapeutic options aim to improve outcomes through earlier definitive diagnosis and preemptive targeted treatment.

Razia D, et al. (2022). Carfilzomib versus rituximab for treatment of de novo donor-specific antibodies in lung transplant recipients. Transplant immunology, 75, 101703. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36049718/

- Retrospective single center review comparing CLAD-free survival and the degree and duration of DSA depletion after treatment of LTRs with CFZ or RTX. Although both CFZ and RTX reduced the MFI of circulating DSAs, RTX prolonged the time to DSA rebound. Despite more pronounced improvement in FEV1 with RTX, there was comparable CLAD-free survival between the 2 groups.

Pham C, et al. (2021). Assessment of Carfilzomib Treatment Response in Lung Transplant Recipients With Antibody-mediated Rejection. Transplantation direct, 7(4), e680. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33748409/

- Retrospective review of 28 LTR with 31 AMR episodes treated with CFZ. A positive response was observed in 74.4% of AMR episodes and 82.1% of patients. This response was driven by loss of complement 1q fixation (70.6%), elimination of class I DSAs (78.6%), and reduction in both classes I (median 2815, 79.5% reduction from baseline) and II DSA mean fluorescence intensity (3171, 37.1%).

Yamanashi K, et al. (2020). Outcomes of combination therapy including rituximab for antibody-mediated rejection after lung transplantation. Gen Thorac Cardiovasc Surg. 68(2): 142-149. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31435872/

- Single center, retrospective study of 8 lung transplant recipients who received combination therapy including rituximab. Two were classified as having clinically definite antibody medicated rejection. Three patients demonstrated decrease in intensity of DSA.

Parquin F, et al (2020). C1-esterase inhibitor treatment for antibody-mediated rejection after lung transplantation: two case reports. European Respiratory Journal. 55(5):1902027. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32079639/

- Case report of two patients treated with C1 esterase inhibitor as part of salvage therapy for probable or possible AMR with complement involvement. Initial therapy comprised plasma exchange, IVIG, rituximab, and pulsed steroids. Both patients were treated with 20 units/kg daily for three days followed by 20 units/kg twice a week for 6 months, and both received concurrent monthly IVIG while on C1 esterase inhibitor maintenance. One patient attained lasting improvement in respiratory function and the other achieved clinical stability for re-transplant.

Ius, F, et al. (2020). Six-year experience with treatment of early donor-specific anti-HLA antibodies in pediatric lung transplantation using a human immunoglobulin-based protocol. Pediatric Pulmonology. 55(3):754-764. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31909902/

- Retrospective review of successive immune gloublin infusions for treatment of early donor specific antibodies (eDSA) in pediatric lung transplant patients, defined by authors as possible subclinical AMR. Patients received IVIG or IgGAM (enriched IgG, IgM, and IgA).

Over a 6 year period, 27 patients received immune globulin for eDSA and were compared against 38 patients with no eDSA. Notably, 14 (52%) of patients received plasma exchange and 25 (93%) received a single dose of rituximab along with immune globulin. Over median follow-up of 28 months, 25 (93%) had clearance of eDSA with 3 (12%) having recurrence of same DSA. Outcomes regarding graft survival, patient survival, biopsy proven rejection, and CLAD development were not statistically different.

Hulbert A, et al (2018). Current challenges and opportunities in the management of antibody-mediated rejection in lung transplantation. Curr Opin Organ Transplant. 23(3):308-315. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29742565/

- Review highlighting recently developed AMR diagnostic criteria in lung transplantation, potential mechanisms that mediate the development of AMR, and current and recent treatment strategies

Ensor CR, et al. (2017). Proteasome inhibitor carfilzomib-based therapy for antibody mediated rejection of the pulmonary allograft: Use and short-term findings. Am J Transplant. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28173620

- Description of 14 lung transplant recipients undergoing AMR treatment with carfilzomib, plasma exchange, and IVIG. Median DSA C1q MFI dropped significantly after therapy and response was sustained at two weeks after therapy. Responders to carfilzomib had less chronic lung allograft dysfunction (CLAD) versus nonresponders.

Vacha M, et al. (2016). Antibody Depletion Strategy for the Treatment of Suspected Antibody Mediated Rejection in Lung Transplant Recipients: Does it work? Clinical Transplantation. 31(3). Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27988971

- An evaluation of an institution-specific protocol for treating suspected antibody mediated rejection in sixteen lung transplant recipients with documented donor specific antibody (DSA) present and allograft dysfunction. A minority of patients had preserved lung function and cleared their DSAs at 6 months following treatment with protocol.

Levine D, et al. (2016). Antibody-mediated rejection of the lung: A consensus report of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant, 35(4): 397-406. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27044531

- Consensus paper on the diagnostic criteria and definition of antibody-mediated rejection in lung transplant recipients.

Kulkarni HS, et al. (2015). Antibody-mediated Rejection in Lung Transplantation. Current Transplantation Reports, 2 (4), 316-323. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27896040

- A review of challenges with diagnosing antibody mediated rejection (AMR) and describes therapeutic options for treating AMR in lung transplant recipients.

Witt C, et al. (2013). Acute antibody-mediated rejection after lung transplantation. The Journal of Heart and Lung Transplantation, 32(10), 1034-40. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23953920

- A single-center, retrospective study that identified patients with acute AMR and assessed their treatment regimens and other clinicopathological details to correlate clinical outcomes, including development of chronic lung allograft dysfunction, and survival.

Daoud A, et al. (2013). Diagnosis and treatment of antibody mediated rejection in lung transplantation: A retrospective case series. Transplant Immunology, 1-5. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23220148

- A single center retrospective study that reviewed all lung transplant patients and identified those who had at least one marker of antibody mediated rejection to assess treatment therapies and outcomes.

Baum C, et al. (2013). Bortezomib rescue therapy in a patient with recurrent antibody mediated rejection after lung transplantation. The Journal of Heart and Lung Transplantation, 32(12), 1270-1271. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/24041981

- Case report describing a patient's successful use of bortezomib therapy for recurrent AMR after lung transplant.

Neumann J, et al. (2010). Acute Humoral Rejection in a Lung Recipient: Reversion With Bortezomib. Transplantation, 89(1), 125-6. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/20061929

- Case report of the first case with the successful use of bortezomib for antibody mediated rejection in a lung transplant recipient

Morrell M, et al. (2009). Acute antibody-mediated rejection after lung transplantation. The Journal of Heart and Lung Transplantation, 28, 96-100. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/19134538

- Case report of a patient with successfully treated acute antibody-mediated rejection after lung transplantation with pulse-dose steroids, immune globulin, plasma exchange and rituximab.

6.5 Retransplant/graft failure

6.5.1 General retransplant/graft failure

Harhay MO, et al. (2022). Epidemiology, risk factors, and outcomes of lung retransplantation: An analysis of the International Society for Heart and Lung Transplantation Thoracic Transplant Registry. J Heart Lung Transplant. 41(10), 1478–1486. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35933297/

- Retrospective cohort ISHLT registry study of LTR receiving their first retransplant(n=1597). Retransplants comprise approximately 4-6% of annual lung transplants worldwide. Six-month and 1 year survival (82% and 76%) were higher for double-double lung retransplant recipients than for single-single recipients (76% and 69%). The three factors most strongly associated with 1 year mortality in this population were the duration of time since the primary lung transplant (decreasing hazard as more time elapses), donor age (increasing hazard with older age), and need for mechanical ventilation re-transplant

Aggarwal R, et al. (2022). Time since primary transplant and poor functional status predict survival after redo lung transplant. Journal of thoracic disease, 14(10), 3819–3830. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36389317/

- Retrospective study of 739 redo lung transplants with 2 groups based on time between redo transplants (<1-year vs. 1+ years). Patients were also grouped based on functional status using the Karnofsky Performance Status (KPS). KPS 10–40% were less likely to be discharged after primary transplant and more likely required mechanical ventilation or

extracorporeal membrane oxygenation (ECMO) bridging (P<0.001). Redo lung transplant survival was worse in the KPS 10-40% group who more likely underwent lung transplant <1 year after primary lung transplant. Mortality was significantly higher for patients who underwent redo lung transplant within one year of primary transplant when KPS was 10-40% (P<0.001).

Ren DR, et al. (2018). Retransplantation outcomes at a large lung transplantation program. Transplant Direct. 4(11):e404. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30534595/

- Single-center retrospective cohort study of lung transplantation recipients. Retransplant was associated with significantly higher mortality after 6 months post-transplant.

Halloran K, et al. (2018). Comprehensive outcomes after lung retransplantation: a single center review. Clinical Transplantation. 32(6): e13281. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29754418

- Retrospective cohort study of adult lung retransplants identified a more complicated post-transplant course following retransplantation with longer ventilation time and ICU stay in addition to lower peak lung function. Quality of life, renal function, microbiology, and DSA formation were similar, and median survival was numerically shorter.

Beliaev AM, et al. (2018). Socioeconomic deprivation is not associated with reduced survival of lung transplant recipients. Journal of Surgical Research. 230:1-6. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/30100023

- Retrospective cohort study over 23 years of 233 lung transplant recipients in New Zealand were classified into two groups using a Deprivation Index Score. Socioeconomic status had no negative effect on rejection, CLAD, or patient survival.

Tangaroonsanti A, et al. (2017). Impaired esophageal motility and clearance post-lung transplant: risk for chronic allograft failure. Clinical and Translational Gastroenterology. 8(6): e102. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28662022

- 50 lung transplant recipients underwent manometry and esophageal motility abnormalities were classified by the Chicago Classification v3.0. Esophagogastric junction outflow obstruction, incomplete bolus transit, and proximal reflux each increased risk of CLAD even though junction outflow obstruction was not associated with a greater number of reflux events. Esophageal dysmotility, more so than reflux alone, may be a risk for CLAD.

Schumer EM, et al. (2017). Single versus double lung retransplantation does not affect survival based on previous transplant type. Annals of Thoracic Surgery, 103(1):236-240. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27677564

- Multicenter retrospective review demonstrated no significant difference in graft survival between recipients of retransplant with single or double lungs when stratified by previous transplant type.

Hall DJ, et al. (2017). Two decades of lung retransplantation: a single-center experience. Annals of Thoracic Surgery, 103(4):1076-1083. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28017335

- Single center retrospective review of lung retransplantion over a 19-year period. Survival was found to be significantly worse in retransplanted patients compared to primary transplant patients.

Baldwin MR, et al. (2013). Donor age and early graft after transplantation: a cohort study. American Journal of Transplantation, 13(10):2685-95. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/24034167

- A retrospective study that evaluated the association between lung donor age and primary graft dysfunction.

Strueber M, et al. (2006). Long-term outcome after pulmonary retransplantation. Journal of Thoracic and Cardiovascular Surgery, 132(2):407–412. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/16872970

- This study reviewed patients with lung retransplant due to various indications. Results of retransplant data versus those of first-time lung transplant were no different.

Brugière O, et al. (2003). Lung retransplantation for bronchiolitis obliterans syndrome: longterm follow-up in a series of 15 recipients. Chest, 123(6):1832–1837. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/12796157

- This study retrospectively reviewed patients with lung retransplantation due to BOS over a 14-year period. Endpoints for survival, causes of death, long-term functional status, and BOS recurrence rate had positive results following retransplantation.

Novick RJ, et al. (1998). Pulmonary retransplantation: predictors of graft function and survival in 230 patients. Pulmonary Retransplant Registry. Annals of Thoracic Surgery, 65(1):227–234. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/9456123

- This multi-center study reviewed certain patient selection criteria and correlated it to retransplantation success.

6.5.2 Primary graft dysfunction

Yuenger V, et al. (2023). Impact of pre-lung transplant statin use on the development of primary graft dysfunction [published online ahead of print, 2023 Jan 31]. Pharmacotherapy. 10.1002/phar.2770. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36722027/

- A retrospective cohort study was performed evaluating all patients undergoing bilateral lung transplantation from September 2012 to December 2019. Of the 357 patients included in the study, 107 received statin therapy prior to transplant (statin group) and 250 did not (no statin group). PGD occurred in 257 (72%) patients; in the entire cohort, 99 (28%) patients experienced PGD grade 1, 59 (17%) grade 2, and 99 (28%) grade 3. A significantly lower incidence of PGD was observed in the statin group (64.5% vs 75.2%, p = 0.039); however, the association did not remain significant on multinominal analysis for an overall incidence of any PGD (p = 0.275) or incidence of severe PGD (p = 0.240). Statin intensity was not associated with the development of PGD. Pre-transplant statin therapy did not appear to impact the development of PGD following lung transplantation.

Toyoda T, et al. (2023). Recipient, donor, and surgical factors leading to primary graft dysfunction after lung transplant. J Thorac Dis. 2023;15(2):399-409. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36910052/

- A retrospective review of the institutional lung transplant database from March 2018 to September 2021 was performed. Primary graft dysfunction grade 1 to 3 occurred in 45.0% of the cohort (n=68) of whom 33.3% (n=23) had primary graft dysfunction grade 3. Longer operative time was more common in primary graft dysfunction grade 1 to 3 patients

(P<0.001). The 1-year survival of the patients with primary graft dysfunction grade 3 was lower than the others (grade 0-2 vs. 3, 93.7% vs. 65.2%, P=0.0006). Univariate analysis showed that acute respiratory distress syndrome, operative time, and intraoperative veno-arterial extracorporeal membrane oxygenation use were risk factors for primary graft dysfunction grades 1 or 2 and grade 3. Multivariate analysis identified that intraoperative veno-arterial extracorporeal membrane oxygenation use was an independent risk factor of primary graft dysfunction grade 1 or 2. Patients with an operative time of more than 8.18 hours had significantly higher incidence of primary graft dysfunction grade 3, acute kidney injury, and digital ischemia.

Chen Q, et al. (2023). Venoarterial or Venovenous Extracorporeal Membrane Oxygenation for Severe Primary Graft Dysfunction after Lung Transplant? [published online ahead of print, 2023 Feb 4]. Ann Thorac Surg. 2023;S0003-4975(23)00102-9. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36746330/

- This is a single-center retrospective cohort study of patients undergoing lung transplantation. Of 773 lung transplant recipients, PGD grade 3 developed in 204 (26%) at any time in the first 72 hours after lung transplantation. Of these, 13 (5%) required VA ECMO and 25 (10%) required VV ECMO support. The 30-day, 1-year, and 5-year survival in the VA ECMO group was 62%, 54%, and 43% compared with 96%, 84%, and 65% in the VV ECMO group and 99%, 94%, and 71% in the non-ECMO group. Multivariable Cox regression analysis showed that VA ECMO was associated with increased mortality (hazard ratio, 2.37; 95% CI, 1.06-5.28; P=0.04).Patients who required VA ECMO support for PGD grade 3 have significantly worse survival compared with those who did not require ECMO and those who required VV ECMO support. This suggests that VA ECMO treatment of patients with PGD grade 3 after lung transplantation can be a predictable risk factor for mortality.

Avtaar Singh SS, et al. (2023). Primary graft dysfunction following lung transplantation: From pathogenesis to future frontiers. World J Transplant. 2023;13(3):58-85.Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36968136/

- This review aims to provide an in-depth analysis of the epidemiology, patho physiology, risk factors, outcomes, and future frontiers involved in mitigating primary graft dysfunction. The current diagnostic criteria are examined alongside changes from the previous definition. We also highlight the issues surrounding chronic lung allograft dysfunction and identify the novel therapies available for ex-vivo lung perfusion. Although primary graft dysfunction remains a significant contributor to 90-d and 1-year mortality, ongoing research and development abreast with current technological advancements have shed some light on the issue in pursuit of future diagnostic and therapeutic tools.

Van Slambrouck J, et al. (2022). A Focused Review on Primary Graft Dysfunction after Clinical Lung Transplantation: A Multilevel Syndrome. Cells. Feb 21;11(4):745. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35203392/

- Review on clinical, physiological, radiological, histological and cellular level of PGD.

Chacon-Alberty L, et al. (2022). Effect of intraoperative support mode on circulating inflammatory biomarkers after lung transplantation surgery. Artificial organs, 10.1111/aor.14474. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36445099/

- Single center retrospective study analyzed cytokine expression profiles after reperfusion and allograft outcomes in a cohort of patients (n=59) who underwent LTR off-pump (n=26), with

cardiopulmonary bypass (CPB; n=18). PGD3 was present at 48 or 72 h after reperfusion in 7.7% (2/26) of off-pump cases, 20.0% (3/15) of ECMO cases, and 38.9% (7/18) of CPB cases (p = 0.04). Cytokine expression profiles after reperfusion were not significantly different between ECMO and CPB groups.

Calabrese F, et al. (2022). Evaluation of Tissue Ischemia/Reperfusion Injury in Lung Recipients Supported by Intraoperative Extracorporeal Membrane Oxygenation: A Single-Center Pilot Study. Cells, 11(22), 3681. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36429108/

- Retrospective single-center observational study of bilateral LTR from 2012-2018. Tissue analyses were performed on the biopsies at the time of transplantation. Lung samples from the ECMO group (both pre- and post-reperfusion) were comparable, or for some parameters better, than samples from the non-ECMO group. Leukocyte margination was significantly lower in the ECMO group than in the non-ECMO group. Primary graft dysfunction, mainly at 24 and 48h, was correlated with the tissue injury score of the post-reperfusion biopsy.

Criner RN, et al. (2021). Primary graft dysfunction. Curr Opin Organ Transplant. Jun 1;26(3):321-327. Retreived from: https://pubmed.ncbi.nlm.nih.gov/33938469/

- Review of definitions, pathophysiology, risk factors, prevention, treatment strategies, and future research directions on PGD.

Clausen E, et al. (2021). Primary graft dysfunction: what we know. J Thorac Dis. Nov;13(11):6618-6627. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34992840/

- Review discusses the understanding of PGD and future directions for research.

Mazo C, et al. (2019). Pneumonia vs. Graft dysfunction as the cause of acute respiratory failure after lung transplant: a 4- year multicenter prospective study in 153 adults requiring intensive care admission. Eur Respir J. 543):1801512. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31346003/

- Five center prospective cohort study in Spain that enrolled all adult lung transplant patients with ICU readmissions after post-transplant ICU discharge. Graft rejection caused 10.8% of readmissions and pneumonia caused 36% of readmissions. Multivariate analyses identified bronchiolitis obliterans syndrome stage 2, restrictive allograft syndrome, and pneumonia at ICU readmissions as independent predictors of ICU mortality.

Bellier J, et al. (2019). Extracorporeal membrane oxygenation for grade 3 primary graft dysfunction after lung transplantation: long-term outcomes. Clin Transplant. 33(3);e13480. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30657612/

- Single-center retrospective study of lung transplant recipients. Patients requiring VA-ECMO had initial increased mortality, but comparable long-term survival.

Shah R, Diamond J (2018). Primary graft dysfunction (PGD) following lung transplantation. Semin Respir Crit Care Med. 39(2): 148-154. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29590671/

- Review article summarizing advances in understanding of PGD, updates in PGD classification and definition, and current controversies surrounding PGD.

Liu Y, et al. (2014). Recipient-related clinical risk factors for primary graft dysfunction after lung transplantation: a systematic review and meta-analysis. PLoS One. Mar 21;9(3):e92773. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/24658073/

- Systematic review discussing risk factors for PGD in lung transplantation. Female gender, African American, idopathic pulmonary fibrosis, sarcoidosis, pHTN, elevated BMI, and use of cardiopulmonary bypass were increased risks for PGD.

Diamond JM, Lung Transplant Outcomes Group et al. (2013). Clinical risk factors for primary graft dysfunction after lung transplantation. Am J Respir Crit Care Med. Mar 1;187(5):527-34. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/23306540/

- This study sought to identify donor, recipient, and perioperative risk factors for PGD. Risk factors included: smoking, FiO2 during allograft reperfusion, single lung transplant, use of cardiopulmonary bypass, overweight/obesity, BMI, preoperative sarcoidosis and mea PAP were risk factors for PGD.

Lee JC, et al. (2011). Primary graft dysfunction. Clin Chest Med. Jun;32(2):279-93. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/21511090/

- Review of PGD epidemiology, outcomes, and risk factors, and to summarize current efforts at biomarker development and novel strategies for prevention and treatment.

Lee JC, et al. (2010). Primary graft dysfunction: definition, risk factors, short- and long-term outcomes. Semin Respir Crit Care Med. Apr;31(2):161-71. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/20354929/

- This review discusses the current definition, contributing factors, and guidelines for grading clinical PGD.

Bermudez C, et al (2009). Extracorporeal membrane oxygenation for primary graft dysfunction after lung transplantation: Long-term survival. The Annals of Thoracic Surgery, 87, 854-860. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/19231405

- A study over a 15-year period that assessed the use of ECMO for primary graft dysfunction post-transplant (within POD#7) and reviewed survival outcomes of that with patients who did not require ECMO.

Prekker ME, et al. (2006). Validation of the proposed International Society for Heart and Lung Transplantation grading system for primary graft dysfunction after lung transplantation. J Heart Lung Transplant. Apr;25(4):371-8. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/16563963/

- Retrospective study assessing the scoring system created for PGD and to compare the performace criteria for the arterial oxygenation to fraction of inspired oxygen. This study showed that grading system can rapidly identify patients with poor outcomes who may benefit from early, aggressive treatment.

Oto T, et al. (2006). Definitions of primary graft dysfunction after lung transplantation: differences between bilateral and single lung transplantation. J Thorac Cardiovasc Surg. Jul;132(1):140-7. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/16798314/

- This study investigates the features and utility of the new primary graft dysfunction grading system by comparing early outcomes from bilateral and single lung transplantation. This study showed that outcomes in bilateral and singular transplant should be considered separately.

Carter YM, et al. (2006). Primary graft dysfunction in lung transplantation. Semin Respir Crit Care Med. Oct;27(5):501-7. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/17072798/

- Discusses PGD mechanisms and successful strategies for treatment and prevention.

Shargall Y, et al. (2005). Report of the ISHLT Working Group on Primary Lung Graft Dysfunction Part VI: Treatment. The Journal of Heart and Lung Transplantation, 24, 1489-1500. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/16210120

- A summary of management strategies for post-op care in lung transplant recipients demonstrating post-transplant primary graft dysfunction.

6.6. Management of Chronic Lung Allograft Dysfunction

Lo WK, et al. (2023). Routine Reflux Testing Guides Timely Anti-reflux Treatment to Reduce Acute and Chronic Rejection After Lung Transplantation. Clinical and translational gastroenterology, 14(1), e00538. https://pubmed.ncbi.nlm.nih.gov/36201668/

- Retrospective cohort study of lung transplant recipients at a tertiary center where all patients underwent pre-transplant ambulatory pH monitoring. Patients were separated into 3 groups: normal pH monitoring (-pH), increased reflux (+pH) with timely treatment, and +pH with delayed treatment. The +pH/delayed treatment patients had higher risks of acute rejection BOS, and CLAD than +pH/timely treatment patients. Rejection risks were increased among +pH/delayed treatment patients vs -pH patients. Timely anti-reflux treatment, as directed by pre-transplant reflux testing, was associated with reduced allograft rejection risks and demonstrated non-inferiority to patients without reflux. A standardized peri-transplant test-and-treat algorithm may guide timely reflux management to improve lung transplant outcomes.

Keller M, et al. (2023). Preemptive treatment of de novo donor-specific antibodies in lung transplant patients reduces subsequent risk of chronic lung allograft dysfunction or death. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons, S1600-6135(22)30224-1. Advance online publication. https://pubmed.ncbi.nlm.nih.gov/36732088/

- Multicenter, retrospective cohort study to determine if early treatment of dnDSAs in lung transplant patients reduces the risk of the composite endpoint of CLAD or death. In the cohort of 445 patients, 145 patients developed dnDSAs post-transplant. Early treatment of dnDSAs was associated with a decreased risk of CLAD or death. Deferring treatment until the development of clinical AMR was associated with an increased risk of CLAD or death. This study suggests that early, preemptive treatment of DSAs may reduce the subsequent risk of CLAD or death.

Geng-Cahuayme AAA, et al. (2023). Efficacy and safety of total lymphoid irradiation in different chronic lung allograft dysfunction phenotypes. Clinical transplantation, 37(2), e14891. https://pubmed.ncbi.nlm.nih.gov/36583252/

- Single-center study included patients with CLAD (29 BOS, 9 RAS, 2 mixed) treated with TLI. Significant attenuation of FEV1 decline slope was observed in all phenotypes and there were no dropouts due to radiation toxicity. TLI may stop FEV1 decline in both BOS and RAS and a good KPS score may be an important prognostic factor.

Evans RA, et al. (2022). Pharmacotherapy of chronic lung allograft dysfunction post lung transplantation. Clin Transplant. Aug;36(8):e14770. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35801376/

- Comprehensive review of literature to prevent and manage CLAD.

Cristeto Porras M., et al. (2023). Early onset of azithromycin to prevent CLAD in lung transplantation: Promising results of a retrospective single centre experience. Clinical transplantation, 37(1), e14832. https://pubmed.ncbi.nlm.nih.gov/36217992/

- Single-center retrospective study, including LT recipients stratified into four groups: those who started AZI at the third week post-LT, those who received AZI later than the third week post-LT and had preserved FEV1, those who did not receive AZI, and those who started AZI due to a decline in FEV1. Initiation of AZI prior to FEV1 decline was protective against CLAD after adjusting for differences between the treatment groups. Early initiation of AZI in LT recipients could have a role in decreasing the incidence and severity of CLAD.

Bos S, et al. (2022). Effector immune cells in chronic lung allograft dysfunction: A systematic review. Immunology, 166(1), 17–37. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35137398/

- Systematic review to comprehensively assess current evidence on effector immune cells in lung tissue and bronchoalveolar lavage fluid from lung transplant recipients with CLAD. 76 studies met criteria for inclusion in analysis. The review summarizes the complex multifactorial immunopathology of CLAD onset and progression. It also highlights the phenotype of several key effector immune cells involved in CLAD pathogenesis, as well as the paucity of single cell resolution spatial studies in lung tissue from patients with CLAD.

Kotecha S, et al. (2021). Outcomes Following ATG Therapy for Chronic Lung Allograft Dysfunction. Transplant Direct. 7(4): e681. https://pubmed.ncbi.nlm.nih.gov/33748410/

- Single center review of antithymocyte globulin (ATG) as second-line therapy for CLAD. Rate of FEV1 decline was calculated before and after ATG. Seventy-one patients were included in the analysis. Sixteen (23%) were complete responders, 29 (40%) were partial responders, and 26 (37%) did not respond. Authors concluded that ATG appears to stabilize or attenuate lung function decline in CLAD.

Vazirani J, et al. (2020). Outcomes Following Extracorporeal Photopheresis for Chronic Lung Allograft Dysfunction Following Lung Transplantation: A Single-Center Experience. Transplant Proc. In press: 1-7. Retrieved from: https://doi.org/10.1016/j.transproceed.2020.09.003

- Retrospective single center case series including 12 lung transplant recipients treated for CLAD with extracorporeal photopheresis (ECP). 67% of patients responded to ECP therapy with a significantly improved mean decline in FEV1 post-treatment.

Trindade AJ, et al. (2020). Alemtuzumab as a Therapy for Chronic Lung Allograft Dysfunction in Lung Transplant Recipients with Short Telomeres. Front Immunol. 11: 1063. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32547557/

- Single center retrospective case series of three lung transplant recipients with telomeropathies treated for CLAD with alemtuzumab. Alemtuzumab was safe in this patient population, however was associated with an increased incidence of neutropenia, thrombocytopenia, and anemia requiring transfusion compared to lung transplant recipients without telomeropathies.

Li D, et al. (2020.) Azithromycin prophylaxis after lung transplantation is associated with improved overall survival. J Heart Lung Transplant. 39(12):1426-1434. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33041181/

- Single center retrospective study that included double lung transplant recipients who received azithromycin prophylaxis and those who did not. Patients who received

azithromycin had improved survival and baseline function compared to those who did not receive azithromycin. Rates of CLAD were not different.

Kotecha S, et al. (2020). An update on chronic lung allograft dysfunction. Ann Transl Med. Mar;8(6):417. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32355861/

- Review discusses definition of CLAD, evolution of CLAD, and future directions for treatment of CLAD.

Girgis R, et al. (2020). Alemtuzumab for chronic lung allograft dysfunction. CHEST, 158(4): A2388. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7550127/

- Retrospective single center case series of eight consecutive lung transplant recipients treated with single subcutaneous alemtuzumab for CLAD. Rate of FEV1 decline significantly improved 3 months post vs 3 months prior to alemtuzumab. Mild to moderate infection occurred in four patients, severe infection occurred in one patient. Two patients died due to progressive CLAD.

Dellgren G, et al. (2020). Design and Rationale of a Scandinavian Multicenter Randomized Study Evaluating if Once-Daily Tacrolimus Versus Twice-Daily Cyclosporine Reduces the 3-year Incidence of Chronic Lung Allograft Dysfunction After Lung Transplantation (ScanCLAD Study). Advances in Therapy. 37: 1260-1275. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31993943/

- Investigator-initiated, randomized, open-label, multicenter trial in lung transplant recipients to assess the incidence of CLAD with once-daily tacrolimus-based vs cyclosporine-based maintenance immunosuppression. Enrollment is ongoing with expected follow up to complete 2022.

Beach SL, et al. (2020). Fungal Prophylaxis and Chronic Lung Allograft Dysfunction. J Heart Lung Transplant. 39(4): S303-S304. Retrieved from: https://www.sciencedirect.com/science/article/abs/pii/S1053249820306963

- Single center retrospective study including lung transplant recipients in two groups: historical targeted antifungal prophylaxis and universal antifungal prophylaxis. There was no difference in freedom from CLAD at 3 years between universal vs targeted prophylaxis, nor based on antifungal agent selected.

Vos R, et al. (2019). Montelukast in chronic lung allograft dysfunction after lung transplantation. J Heart Lung Transplant. 38(5): 516-527. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30638839/

- Retrospective single center study of lung transplant recipients with progressive CLAD, despite 3 months of azithromycin use, treated with montelukast. Montelukast associated with significantly improved FEV1 rate of decline at 3 and 6 months. Patients whose FEV1 improved or stabilized had significantly improved progression-free and overall survival.

Verleden GM, et al. (2019). 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. 38(5): 493-503. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30962148/

- Consensus report to standardize and refine nomenclature of CLAD and clinical phenotypes.

Van Herck A, et al. (2019). Azithromycin and early allograft function after lung transplantation: A randomized, controlled trial. J Heart Lung Transplant. 38(3):252-259. https://pubmed.ncbi.nlm.nih.gov/30686699/

- A prospective, randomized, placebo-controlled trial of pre-transplant and prompt initiation of azithromycin post-transplant in the treatment arm (placebo n=34, azithromycin n=34). Primary outcome was an anticipated 15% improvement of forced expiratory volume in 1 second (FEV1) during the first 3 months post-transplant. FEV1 was not significantly different between groups (p = 0.41).

January SE, et al (2019). Rabbit antithymocyte globulin for the treatment of chronic lung allograft dysfunction. Clinical Transplantation. 33e13708. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31494969/

- Single-center retrospective cohort study of lung transplant recipients (n=108) treated with rATG for CLAD. Treatment with rATG was associated with reversal in the decline of lung function (increase of FEV1) in 40% of patients. Serum sickness, cytokine release syndrome, and infection after therapy developed in 22%, 15%, and 19% of patients, respectively.

Glanville AR, et al (2019). Chronic lung allograft dysfunction: Definition and update of restrictive allograft syndrome- A consensus report from the Pulmonary Council of ISHLT. J Heart Lung Transplant. 38(5): 483-492. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31027539/

- Consensus report with standardized definition and understanding of RAS.

Keller CA, et al. (2018). Feasibility, Safety, and Tolerance of Mesenchymal Stem Cell Therapy for Obstructive Chronic Lung Allograft Dysfunction. Stem Cells Transl Med. 7(2): 161-167. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29322685/

- Prospective feasibility study of allogeneic mesenchymal stem cell (MSC) therapy feasibility and safety in nine lung transplant recipients with bronchiolitis obliterans syndrome (BOS) refractory to standard therapy. Up to 1 month of follow up, there was no change in gas exchange, pulmonary function tests, or routine labs suggesting MSC therapy is safe. Further studies are needed to assess efficacy

Szczepanik A, et al. (2018). Effect of HMG CoA reductase inhibitors on the development of chronic lung allograft dysfunction. Clin Transplant. 32(1): e13156. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29151274/

- Single center study assessing statin use and development of CLAD. Statin use was not associated with decreased risk of CLAD at 3 years but demonstrated decreased risk of death. At 3 years, patient survival was 81.7% in statin group and 68.3% in nonstatin group (P=.012)

Moniodis A, et al. (2018). Comparison of extracorporeal photopheresis and alemtuzumab for the treatment of chronic lung allograft dysfunction. J Heart Lung Transplant. 37(3): 340-348. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/28431983/

- Retrospective single center analysis of lung transplant recipients with CLAD who were treated with extracorporeal photopheresis (ECP), alemtuzumab, or no treatment. Rate of FEV1 decline was significantly improved after either treatment, however no difference in FVC was seen. There was no difference in infection rates or survival after treatment. Comparison with no treatment was limited due to significant clinical differences between groups, however no difference in mean FEV1 slope difference was identified.

Verleden SE, et al. (2017). Chronic lung allograft dysfunction phenotypes and treatment. J Thorac Dis. Aug;9(8):2650-2659. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/28932572/

- Overview of treatment strategies for CLAD.

Boettcher H, et al. (2002). Methotrexate Rescue Therapy in Lung Transplantation. Transplantation Proceedings, 34, 3255-3257. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12493438

- Analysis of a single center experience with methotrexate in five lung transplant recipients with steroid-resistant acute rejection episodes or in lung transplant patients with recurrent rejection or bronchiolitis obliterans syndrome.

6.6.1 Bronchiolitis obliterans syndrome

Neurohr C, et al. (2022). A randomized controlled trial of liposomal cyclosporine A for inhalation in the prevention of bronchiolitis obliterans syndrome following lung transplantation. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons, 22(1), 222–229. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34587371/

- Randomized, double-blind, placebo-controlled, multi-center Phase 3 study, 180 LT recipients in BOS grade 0 were planned to receive L-CsA-i or placebo in addition to triple-drug immunosuppression. The primary endpoint was BOS-free survival. 130 patients were enrolled before the study was prematurely terminated for business reasons. Despite a 2-year actuarial difference in BOS-free survival of 14.1% in favor of L-CsA-i in the overall study population, the primary endpoint was not met (p = .243). The pre-defined per protocol analysis of SLT recipients (n = 24) resulted in a treatment difference of 58.2% (p = .053). No difference was observed in the BLT (n = 48) subpopulation (p = .973). L-CsA-i inhalation was well tolerated.

Hao X, et al. (2022). Effect of azithromycin on bronchiolitis obliterans syndrome in posttransplant recipients: A systematic review and meta-analysis. Medicine, 101(28), e29160. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35839027/

- Meta-analysis to evaluate the effects of azithromycin on forced expiratory volume in 1 second (FEV1) and patient's survival. 15 eligible studies involving 694 participants were identified. For FEV1 (L), there was a significant increase after short-term (≤12 weeks; P = .00) and mid-term (12-24 weeks; P = .01) administration of azithromycin. There was also a significant increase in FEV1 (%) compared to baseline after short-term administration of azithromycin (P = .02), and no statistically significant differences in the medium and long term. When pooled FEV1% was predicted, it exhibited a similar trend to FEV1 (%) compared to baseline. Azithromycin reduced the risk of death (HR = 0.26; 95% CI = 0.17 to 0.40; P = .00) in patients with BOS post-lung transplantation.

Perch M, et al. (2020). A European Multi-Center, Randomized, Double-Blind Trial of Pirfenidone in Bronchiolitis-Obliterans-Syndrome Grade 1-3 in Lung Transplant Recipients (European Trial of Pirfenidone in BOS (EPOS)). J Heart Lung Transplant. 39(4): S12. Retrieved from: https://www.jhltonline.org/article/S1053-2498(20)31147-5/abstract

- Investigator-initiated, multicenter, randomized, controlled trial including lung transplant recipients with new onset progressive BOS assigned to pirfenidone or placebo for 6 months. Primary endpoint to be assessed is change in FEV1 over 6 months.

Lebeer M, et al. (2020). Total lymphoid irradiation in progressive bronchiolitis obliterans syndrome after lung transplantation: a single-center experience and review of literature. Transplant Int. 33(2):216-228. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31643104/

- Single center retrospective analysis including lung transplant recipients with progressive BOS treated with total lymphoid irradiation (TLI). Treatment was associated with decreased rate of FEV1 decline, particularly in those with rapid decline. Overall patient survival was

44% at two years post-treatment. TLI was generally well-tolerated and may be useful as a bridge to redo transplant in select patients.

Iacono A, et al. (2019). A randomised single-centre trial of inhaled liposomal cyclosporine for bronchiolitis obliterans syndrome post-lung transplantation. ERJ Open Res. 5: 00167. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31687370/

- Phase 2b trial in lung transplant recipients with BOS randomized to either inhaled liposomal cyclosporine (L-CsA) or standard-of-care (SOC) alone. Progression-free survival was non-significantly improved in the L-CsA group. L-CsA group also with improved median survival and stabilized change in FEV1and FVC.

Ruttens D, et al. (2018). Montelukast for bronchiolitis obliterans syndrome after lung transplantation: a randomized controlled trial. PLoS One. 13(4): e0193564. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29624575

- Patients receiving montelukast for BOS did not have differences in graft loss at one year or in acute rejection, lymphocytic bronchiolitis, or respiratory infection rate. However, in a post-hoc subanalysis of stage 1 BOS patients, montelukast had a positive impact on FEV1 decline in the study period.

Hachem R, et al. (2018). Extracorporeal Photopheresis for Bronchiolitis Obliterans Syndrome After Lung Transplantation. Transplantation. 102(7):1059-1065. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29557913/

- Review of literature for ECP as part of BOS management in lung transplant recipients. The mechanism of action is described. Small studies suggest ECP therapy is associated with improved or stabilized lung function, decreased rate of functional decline, and is well-tolerated.

Moore CA, et al. (2017). Effect of aerosolized antipseudomonals on Pseudomonas positivity and bronchiolitis obliterans syndrome after lung transplantation. Transplant Infectious Diseases, 19(3). Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28273385

- Single-center retrospective cohort of patients treated with aerosolized antipseudomonals finding similar time to positive culture results in addition to incidence of culture positivity at one year. Aerosolized antipseudomonals were protective against recurrence in non-CF patients.

Ensor CR, et al. (2017). Rescue alemtuzumab for refractory acute cellular rejection and bronchiolitis obliterans syndrome after lung transplantation. Clinical Transplantation, 31(4). Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28008661

- Rescue alemtuzumab provides transient benefit for lung transplant recipients with BOS I, but recipients with advanced stage BOS seem not to improve with rescue alemtuzumab therapy.

Furuya Y, et al. (2016). The impact of alemtuzumab and basiliximab induction on patient survival and time to bronchiolitis obliterans syndrome in double lung transplantation recipients. American Journal of Transplantation, 16(8): 2334-2341. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/26833657

- Analysis of UNOS data of approximately 6000 recipients demonstrated prolonged median survival with use of alemtuzumab or basiliximab compared to no induction. And a lower incidence of BOS at 5 years with alemtuzumab use.

Copeland CA, et al. (2010). Survival after bronchiolitis obliterans syndrome among bilateral lung transplant recipients. American Journal of Respiratory and Critical Care Medicine, 182(6):784-789. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/20508211

- A single-center study of bilateral lung transplant recipients that describes the factors influencing survival in patients with BOS – including timing and severity of BOS, and its concurrent treatment therapies.

Reams, B et al. (2007). Alemtuzumab in the treatment of refractory acute rejection and bronchiolitis obliterans syndrome after human lung transplantation. American Journal of Transplantation, 7, 2802-2808. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/17924993

- An observational study that evaluated heart-lung or lung patients with refractory acute rejection (RAR) and BOS who failed therapy with steroid and antithymocyte globulin and received rescue alemtuzumab. Histological rejection scores were improved following alemtuzumab administration with freedom from BOS present in 65% of patients with RAR.

Johnson BA, et al. (2003). Statin use is associated with improved function and survival of lung allografts. American Journal of Respiratory and Critical Care Medicine, 167(9):1271-1278. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/12615629

- Single center retrospective study comparing the outcomes of lung transplant recipients prescribed statins vs those who did not receive HMG-CoA reductase inhibitors. Statin use was associated with a lower cumulative incidence of BOS relative to controls and may provide positive pulmonary effects post-transplant.

Gerhardt SG, et al. (2003). Maintenance azithromycin therapy for bronchiolitis obliterans syndrome: results of a pilot study. American Journal of Respiratory and Critical Care Medicine, 168(1):121-125. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/12672648

- An open-label pilot trial involving 6 patients to determine the effect of azithromycin maintenance therapy on improvements in lung function in patients with BOS.

Estenne M, et al. (2002). Bronchiolitis obliterans after human lung transplantation. American Journal of Respiratory and Critical Care Medicine, 166(4):440-444. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/12186817

- A review of current concepts of BOS, overview of pathogenesis and risks factors, methods of early detection, and current and future management therapies.

6.6.2 Restrictive allograft syndrome

Klouda T, et al. (2021). Restrictive allograft syndrome after lung transplantation. Pediatr Transplant. May;25(3):e14000. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33728767/

- Review discusses the efinition, mechanism, and characteristics of RAS.

Pluchart H, et al. (2020). Restrictive allograft dysfunction after lung transplantation: is there a place for nintedanib?—a case report. Fundam Clin Pharmacol. 34(3): 408-411. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31755131/

- Case report of lung transplant recipient with bronchiolitis obliterans syndrome evolved to restrictive allograft syndrome treated with nintedanib 150 mg twice daily. Therapy was discontinued after four months due to gastrointestinal intolerance without clinical improvement.

Sato M, et al. (2013). Progression pattern of restrictive allograft syndrome after lung transplantation. J Heart Lung Transplant. Jan;32(1):23-30. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/23260703/

- Study analyzed progression patterns of RAS. and found a "stair-step" pattern of progression.

Sato M, et al. (2011). Restrictive allograft syndrome (RAS): a novel form of chronic lung allograft dysfunction. J Heart Lung Transplant. Jul;30(7):735-42. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/21419659/

- Retrospective study evaluating CLAD phenotype in lung transplant patients that determined specific characteristics of RAS.

6.7 Lung diseases

6.7.1 Idiopathic pulmonary fibrosis

De Andrade JA, et al. (2023). Effect of Antifibrotic Therapy on Survival in Patients With Idiopathic Pulmonary Fibrosis [published online ahead of print, 2023 Mar 28]. Clin Ther. 2023;S0149-2918(23)00102-9. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36997445/

- Data from a multicenter US registry of patients with IPF were used to assess the effect of antifibrotic therapy (nintedanib or pirfenidone) on death, death or lung transplant, respiratory-related hospitalization, and acute worsening of IPF (defined as any health care encounter deemed due to acute worsening of IPF. Among the 499 patients analyzed, 352 (70.5%) received antifibrotic therapy. Estimated event rates of death at 1 year were 6.6% (95% CI, 6.1-7.1) for treated patients and 10.2% (95% CI, 9.5-10.9) for control patients. There was a numerical reduction in the risk of death (hazard ratio [HR], 0.53; 95% CI, 0.28-1.03; P = 0.060) but numerical increases in risks of respiratory-related hospitalization (HR, 1.88; 95% CI, 0.90-3.92; P = 0.091) and acute worsening of IPF (HR, 1.71; 95% CI, 0.36-8.09; P = 0.496) in treated versus control patients. Overall, analyses based on causal inference methodology suggest that patients with IPF who receive antifibrotic therapy have improved survival.

Astor TL, et al. (2023). Anti-fibrotic therapy and lung transplant outcomes in patients with idiopathic pulmonary fibrosis. Ther Adv Respir Dis. Jan-Dec;17:17534666231165912. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37073794/

- Investigated antifibrotic use discontinuation time and transplant outcomes. Anastomotic and sternal dehiscence only occurred in patients with idiopathic pulmonary fibrosis who discontinued anti-fibrotic therapy < 5 medication half-lives before transplant.

Mora Cuesta VM, et al. (2022). Antifibrotics and lung transplantation: A Spanish multicentre case-controlled study. Respirology (Carlton, Vic.), 27(12), 1054–1063. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36053911

- Retrospective review of IPF patients receiving antifibrotic treatments at the time of lung transplant (103 cases) compared to those who did not receive antifibrotic treatment (61 controls). Patients on antifibrotic drugs experienced earlier onset of wall dehiscence earlier (21 days [IQR = 12.5-41.5] vs. 63 days [IQR = 46.75-152.25]; p = 0.012), although there were no differences in the incidence of wall dehiscence in either group (12.3% vs. 13.7%; p = 0.318There were no differences in overall post-transplant survival or in conditional survival

at 30 days, 90 days, 3 years or 5 years. 1 year survival was significantly greater among controls (80.6% vs. 93.3%; p = 0.028).

Glass DS, et al. (2022). Idiopathic pulmonary fibrosis: Current and future treatment. Clin Respir J. Feb;16(2):84-96. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35001525/

- Review discusses treatment approaches to IPF.

Dorey-Stein ZL, et al. (2021). Effect of antifibrotic therapy in patients with idiopathic pulmonary fibrosis undergoing lung transplant in the peri and post-operative period. Respir Med. Dec;190:106599. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34788735/

- Evaluates use of antifibrotic therapy up to time of lung transplant and rates of complications and mortality. Patients had better preservation of lung function and similar outcomes post-transplant with use of antifibrotics.

Behr J, et al. (2021). Efficacy and safety of sildenafil added to pirfenidone in patients with advanced idiopathic pulmonary fibrosis and risk of pulmonary hypertension: a double-blind, randomised, placebo-controlled, phase 2b trial. Lancet Respiratory Medicine, 9(1):85-95. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32822614/

- RCT of 177 patients with advanced IPF and either at risk for or with high probability of group 3 pulmonary hypertension treated with pirfenidone + placebo or pirfenidone + sildenafil. Patients were followed for 52 weeks for disease progression with a composite endpoint of decline in 6MWD, respiratory-related hospital admission, or all-cause mortality. Progression free survival was not improved with addition of sildenafil, and analysis of individual components of composite endpoint yielded no significant results.

Ranganath NK, et al. (2020). Single and Double Lung Transplantation Have Equivalent Survival for Idiopathic Pulmonary Fibrosis. Ann Thorac Surg. Jan;109(1):211-217. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31445911/

- Analyzed double lung vs single lung transplant for IPF. Single lung transplant required less ventilation time and a trend towards decreased rates of post-transplant renal failure and hospital length of stay.

Iasella CJ, et al. (2020). Idiopathic pulmonary fibrosis lung transplant recipients are at increased risk for EBV-associated posttransplant lymphoproliferative disorder and worse survival. American Journal of Transplantation, 20(5):1439-1446. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31874120/

- Retrospective review of adult lung transplant recipients in single center cohort. Of 611 evaluable patients in the study period, 28 patients (4.6%) developed EBV-associated neoplasia. Despite comprising 22.9% of overall LT population, IPF transplant recipients accounted for 12 (42.9%) of neoplasms. Multivariate Cox proportional hazards model suggested IPF (HR 3.51, 95% CI 1.33-8.21), EBV mismatch, and alemtuzumab induction were independent predictors of PTLD development. When evaluating for early vs late PTLD, diagnosis of IPF was only predictor of late PTLD after matching for age and sex.

Spratt JR, et al. (2019). Single versus bilateral lung transplantation for idiopathic pulmonary fibrosis in the lung allocation score era. Journal of Surgical Research, 234:84-95. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/30527505

- 151 lung transplant recipients (2005-2017) were reviewed for overall, rejection-free, and BOS-free survival at 1 and 5 years. Differences in survival were not statistically significant although bilateral transplant recipients had longer ventilation duration and length of stay post-transplant.

Somogyi V, et al. (2019). The therapy of idiopathic pulmonary fibrosis: what is next? Eur Respir Rev. 28(153):190021. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31484664/

- Review article summarizing new therapeutic agents for IPF and potential future approaches

George PM, et al. (2019). Lung transplantation for idiopathic pulmonary fibrosis. Lancet Respir Med.7(3):271-282. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30738856

- Review article discussing management of IPF comorbidities and the landscape of transplantation for patients with IPF

Kumar A, et al. (2018). Lung transplantation in idiopathic pulmonary fibrosis. Expert Rev Respir Med. May;12(5):375-385. Retreived from: https://pubmed.ncbi.nlm.nih.gov/29621919/

- Review that discusses the potential effect of anti-fibrotic therapy in the pre and post-transplant period, and the need for single or bilateral lung transplant.

Delanote I, et al. (2016). Safety and efficacy of bridging to lung transplantation with antifibrotic drugs in idiopathic pulmonary fibrosis: a case series. BMC Pulmonary Medicine, 16(1): 156. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27863518

- Case series of 9 patients receiving either pirfenidone or nintedanib demonstrated these medications may attenuate disease progression while awaiting a lung transplant.

Chauhan D, et al. (2016). Post-transplant survival in idiopathic pulmonary fibrosis patients concurrently listed for single and double lung transplantation. Journal of Heart and Lung Transplantation, 35(5): 657-60. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/26856664

- Analysis of UNOS data demonstrating no statistical difference in actuarial graft survival between patients undergoing single versus double lung transplant which suggests increased use of single lung transplant may increase the availability of organs to other candidates

Richeldi L, et al. (2014). Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. New England Journal of Medicine, 370(22): 2071-82. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/24836310

- Phase 3 trial demonstrating nintedanib reduces the decline in FVC and thus, slows disease progression.

King TE, et al. (2014). A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. New England Journal of Medicine, 370(22): 2083-92. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/24836312

- Phase 3 study that confirmed pirfenidone reduced disease progression (reflected by lung function, exercise tolerance, and progression-free survival) with idiopathic pulmonary fibrosis.

Noble PW, et al. (2011). Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomized trials. Lancet, 377(9779): 1760-9. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/21571362

- Phase II trial demonstrating pirfenidone, a new, effective anti-fibrotic agent, reduces deterioration in lung function in patients with idiopathic pulmonary fibrosis.

George TJ, et al. (2011). Lung transplant in idiopathic pulmonary fibrosis. Arch Surg. Oct;146(10):1204-9. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/22006881/

- Reviewed trials and case series of lung transplant for IPF.

Mason DP, et al. (2007). Lung transplantation for idiopathic pulmonary fibrosis. Ann Thorac Surg. Oct;84(4):1121-8. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/17888957/

- Compared survival rates and risk factors for patients with IPF vs non-IPF with lung transplantation. Risk factors included earlier date of transplantation, single lung transplant, and higher wedge pressure. Survival after lung transplant for IPF was worse than other indications.

Thabut G, et al. (2003). Survival benefit of lung transplantation for patients with idiopathic pulmonary fibrosis. Journal of Thoracic and Cardiovascular Surgery, 126(2): 469-75. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/12928646

- Overall survival was evaluated in patients with idiopathic pulmonary fibrosis who received or did not receive lung transplantation.

Gross TJ, et al. (2001). Idiopathic pulmonary fibrosis. New England Journal of Medicine, 345(7), 517-525. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/11519507

- Review article describing the pathogenesis of idiopathic pulmonary fibrosis, diagnosis of disease, and treatment options.

Meyers BF, et al. (2000). Single versus bilateral lung transplantation for idiopathic pulmonary fibrosis: a ten-year institutional experience. Journal of Thoracic and Cardiovascular Surgery, 120(1), 99-107. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/10884661

- A retrospective review of outcomes in single and bilateral lung transplant recipients with idiopathic pulmonary fibrosis.

6.7.2 Primary pulmonary hypertension

Ohsumi A, et al. (2022). New strategy to resume and taper epoprostenol after lung transplant for pulmonary hypertension. General thoracic and cardiovascular surgery, 70(4), 372–377. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34978021/

- Retrospective single study review of 23 LTR with severe PH who either abruptly discontinued (n=6) epoprostenol after establishment of extracorporeal circulation or discontinued and resumed epoprostenol after reperfusion then tapered gradually over 2 weeks (n=17). The PGD score was significantly lower in the tapered group than in the discontinued group at 0 h, 24 h, and 48 h after LTx. In addition, the discontinued group required longer mechanical ventilation than the tapered group. Delayed chest closure and post-transplant ECMO use for recovery occurred significantly more frequently in the discontinued group.

Antonczyk R, et al. (2020). Single lung transplant vs double lung transplant: A single-center experience with particular consideration for idiopathic pulmonary arterial hypertension. Transplant Proc. 52(7): 2138-2142. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32474000/

- Retrospective analysis of single vs double lung transplant recipients, 12.3% due to primary pulmonary hypertension. 5-year survival amongst patients with primary pulmonary hypertension was significantly greater in those who received a double lung as compared to single lung transplant. Worst short-term survival of all indications was seen in the primary pulmonary hypertension group.

Zhu S, et al. (2019). Risk analysis of perioperative death in lung transplant patients with severe idiopathic pulmonary hypertension, Transplant Proc. 51(3): 875-879. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30979479/

- Retrospective case-control study of lung transplant recipients with idiopathic pulmonary hypertension assessing perioperative death. Highest risk of death was associated with high frequencies of syncope, hyponatremia, lower cardiac index, inner diameter of left ventricle, and RV/LV ratio.

Rosenzweig EB, et al. (2019). Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Respir J. 53: 1801916. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30545978/

- Task force of World Symposium on Pulmonary Hypertension updates on definition, classification, diagnostics, and treatment of pediatric pulmonary hypertension.

Frost A, et al. (2019). Safety and tolerability of transition from inhaled treprostinil to oral selexipag in pulmonary arterial hypertension: Results from the TRANSIT-1 study. Journal of Heart and Lung Transplant. 38(1): 43-50. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30391194

- Safety and tolerability of selexipag following treprostinil. The study included 34 patients, and 32 were successfully transitioned to selexipag with 28 of those patients meeting criteria for continued therapy. Three patients discontinued therapy due to adverse effects.

Cohen JL, et al. (2019). Sildenafil Use in Children with Pulmonary Hypertension. J Pediatr. 205: 29-34.e1. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30396684/

- Retrospective, single center cohort study of children with pulmonary hypertension treated with sildenafil. 37% remained on sildenafil or tadalafil, 35% discontinued therapy due to improvement, 20% died, and 7% were lost to follow up. Overall sildenafil was well-tolerated.

Taichman DB, et al. (2014). Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST guideline and expert panel report. Chest, 146(2):449-475. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/24937180

- Guideline for pharmacologic therapy for adult patients with PAH as informed by available evidence.

Galiè N, et al. (2013). Updated treatment algorithm of pulmonary arterial hypertension. Journal of the American College of Cardiology, 62(25 Suppl): D60-72. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/24355643

- Treatment algorithm focusing on 3 areas: 1) general measures, supportive therapy, referral strategy, acute vasoreactivity testing and chronic treatment with calcium channel blockers; 2) initial therapy with approved PAH drugs; and 3) clinical response to the initial therapy, combination therapy, balloon atrial septostomy, and lung transplantation.

de Perrot M, et al. (2012). Outcome of patients with pulmonary arterial hypertension referred for lung transplantation: a 14-year single-center experience. Journal of Thoracic and Cardiovascular Surgery, 143(4):910-918. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/22306224

- Retrospective, single center review of all patients transplanted for pulmonary arterial hypertension.

George MP, et al. (2011). Lung transplantation for pulmonary hypertension. Pulmonary Circulation, 1(2): 182-191. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/22034605

- Review article discussing indications for transplant, preparation for transplant and listing, operative issues, and outcomes for patients with pulmonary arterial hypertension.

Humbert M, et al. (2004). Treatment of pulmonary arterial hypertension. New England Journal of Medicine, 351(14): 1425-1436. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/15459304

- Review article describing treatment alternatives according to the various pathophysiologic mechanisms involved with pulmonary arterial hypertension.

Farber HW, et al. (2004). Pulmonary arterial hypertension. New England Journal of Medicine, 351(16): 1655-1665. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/15483284

- Review article describing molecular, environmental, and genetic causes for pulmonary hypertension.

6.7.3 Alpha-1 antitrypsin deficiency

Zamora MR, et al. (2021). Lung and liver transplantation in patients with alpha-1 antitrypsin deficiency. Therapeutic advances in chronic disease, 12_suppl, 20406223211002988. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34408830/

- Review article discussing both lung and liver transplantation and the associated outcomes in patients with AATD, as well as combined lung and liver transplantation.

Riley L, et al. (2020). Clinical outcomes and survival following lung transplantation in patients with Alpha-1 antitrypsin deficiency. Respir Med. 172:106145. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32911139/

- Retrospective review of UNOS data on lung transplants between March 1992 and September 2019. Patients transplanted for AATD had similar long-term survival compared to all other transplant recipients (HR 0.96, 95% CI 0.9-1.02, p=0.19). When adjusting for age, overall survival was improved with AATD patients relative to those with non-AATD related COPD (HR 0.59, CI 0.555-0.64, p<0.001), but risk of death from infection or multi-organ failure was higher in AATD patients. Median survival was better in patients with double lung transplant compared to single lung transplant (7.7 years vs 4.4 years, p </= 0.001).

Spratt JR, et al. (2019). Greater survival despite increased complications rates following lung transplant for alpha-1 antitrypsin deficiency compared to chronic obstructive pulmonary disease. J Thorac Dis.11(4):1130-1144. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31179055

- Single center retrospective cohort study of 385 patients who underwent lung transplant for COPD with or without alpha-1 antitrypsin deficiency (A1AD). A1AD patients were found to have worse short-term complications, but improved long-term survival compared to COPD patients.

Kleinervoa J, et al. (2019). The withdrawal of replacement therapy and outcomes in alpha-a antitrypsin deficiency lung transplant recipients. Eur Respir J. 18;53(5). Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30819816/

- Retrospective review of 222 lung transplant recipients with COPD and AATD. Primary endpoint of incidence of post-transplant complications. Early bronchial anastomotic complications and late bowel complications were observed only in AATD patients.

Gulack BC, et al. (2018). Survival after lung transplantation in recipients with alpha-1-antitrypsin deficiency compared to other forms of chronic obstructive pulmonary disease: a national cohort study. Transpl Int. 31(1):45-55. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/28833662

- UNOS database study which demonstrated patients with A1AD who received a single lung transplant had reduced 1 year survival. For patients who received a bilateral lung transplants there was no significant difference in survival by diagnosis

Edgar RG, et al. (2017). Treatment of lung disease in alpha-1 antitrypsin deficiency: a systematic review. International Journal of Chronic Obstructive Pulmonary Disease, 12:1295-1308. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28496314

- Systematic review of A1AD treatment categorized studies into four groups: COPD medical, COPD surgical, A1AD specific, and other treatments. Concluded that only intravenous augmentation is the only disease-specific therapy in A1AD and can slow emphysema as determined by CT density. Other treatments lack data, and usual COPD treatments may not be effective.

Stone HM, et al. (2016). Lung transplantation in alpha-1-antitrypsin deficiency. COPD: Journal of Chronic Obstructive Pulmonary Disease, 13(2): 146-152. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/26488418

- This study evaluated survival and health benefits in individuals receiving lung transplant for alpha-1 antitrypsin deficiency (A1AT) matched with A1AT patients who did not receive lung transplant. Lung transplant improved quality of life, but did not improve 5year survival.

Tanash HA, et al. (2014). Survival benefit of lung transplantation for chronic obstructive pulmonary disease in Sweden. The Annals of Thoracic Surgery, 98(6): 1930-1935. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/25443001

- This study evaluated survival after lung transplant between alpha-1 antitrypsin deficient (A1AT) individuals with chronic obstructive pulmonary disease (COPD) compared to those without A1AT-related COPD. A significant difference in survival was seen between the two groups at six and twelve years.

Sclar DA, et al. (2012). α1-Proteinase inhibitor (human) in the treatment of hereditary emphysema secondary to α 1-antitrypsin deficiency: number and costs of years of life gained. Clinical Drug Investigation, 32(5): 353-360. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22480280

- Evaluated number of years of life gained and expense per year of life gained in patients receiving augmentation therapy. Augmentation therapy was associated with increase in life years gained with gender and smoking status impacting years of life gained.

Tanash HA, et al. (2011). Survival benefit of lung transplantation in individuals with severe α1-anti-trypsin deficiency (PiZZ) and emphysema. The Journal of Heart and Lung Transplantation, 30 (12): 1342-1347. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/21821433

- This study evaluated survival benefit in patients with alpha-1 antitrypsin deficiency and emphysema receiving lung transplantation and compared outcomes to patients who did not receive lung transplant and continued medical therapy. Lung transplantation was found to significantly improve survival.

Silverman EK, et al. (2009). Alpha1-antitrypsin deficiency. New England Journal of Medicine. 360(26):2749-2757. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19553648

- The article introduces a case vignette and further discusses the pathogenesis of genetic predisposition to alpha1-antitrypsin deficiency, diagnosis of disease, potential treatment options, and areas for research.

6.7.4 Cystic fibrosis

Washington GC, et al. (2023). Use of methylene blue to treat vasoplegia syndrome in cystic fibrosis patients undergoing lung transplantation: A case series. Ann Card Anaesth. 2023;26(1):36-41. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36894412/

- Single-center, retrospective, case series analysis of cystic fibrosis patients who underwent lung transplant and received MB for vasoplegia. No patients developed acute primary graft dysfunction and there was 100% 30-day and 1-year survival. One patient required Extracorporeal membrane oxygenation (ECMO) for hypoxemia and 69% (9/13) of the patients had evidence of postoperative right ventricular dysfunction, but no patients required a right ventricular assist device. This case series demonstrates the effectiveness of MB in treating vasoplegia in cystic fibrosis patients during lung transplantation, without evidence of primary graft dysfunction, 30-day or 1-year mortality.

Gauvreau A, et al. (2023). Post-transplant outcomes among cystic fibrosis patients undergoing lung transplantation colonized by Burkholderia: A single center cohort study [published online ahead of print, 2023 Feb 15]. *J Heart Lung Transplant*. 2023;S1053-2498(23)00040-2. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36894412/

- We conducted a retrospective cohort study which included all consecutive CF-LTR between 2000 and 2019 to compare the postoperative survival of BCC-infected CF lung transplant recipients (CF-LTR) to BCC-uninfected patients. A total of 205 patients were included with a mean age of 30.5 years. Seventeen patients (8%) were infected with BCC prior to LT. Patients were infected with the following species: B. multivorans5, B. vietnamiensis3, combined B. multivorans and B. vietnamiensis3 and others4. None of the patients were infected with B. cenocepacia. Three patients were infected with B. gladioli. One-year survival was 91.7% (188/205) for the entire cohort, 82.4% (14/17) among BCC-infected CF-LTR, and 92.5% (173/188) among BCC uninfected CF-LTR (crude HR = 2.19; 95%CI 0.99-4.85; p = 0.05). In the multivariable model, presence of BCC was not significantly associated with worse survival (adjusted HR 1.89; 95%CI 0.85-4.24; p = 0.12).

Bower JK, et al. (2023). Real-world safety and effectiveness of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis: Interim results of a long-term registry-based study [published online ahead of print, 2023 Mar 22]. J Cyst Fibros. 2023;S1569-1993(23)00066-8. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36963986/

- The study included people with CF in the US Cystic Fibrosis Foundation Patient Registry (CFFPR) who initiated ELX/TEZ/IVA between October 2019 and December 2020. 16,116 people with CF were included (mean treatment duration 20.4 months). ELX/TEZ/IVA treatment was associated with sustained improvements in lung function, reduced frequency

of PEx and all-cause hospitalization, increased BMI, and lower prevalence of positive bacterial cultures. Additionally, there was a 72% lower rate of death and 85% lower rate of lung transplantation relative to the year before ELX/TEZ/IVA availability.

Reams BD, et al (2022). Sublingual tacrolimus for immunosuppression in lung transplantation: a potentially important therapeutic option in cystic fibrosis. Am J Respir Med. 1(2):91-8. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/14720063/

- Evaluated use of sublingual tacrolimus (SL) in cystic fibrosis patients. SL tacrolimus may be beneficial with absorption issues post lung transplant.

Ramos KJ, et al; CFLTC Study Group. (2022). Use of elexacaftor/tezacaftor/ivacaftor among cystic fibrosis lung transplant recipients. J Cyst Fibros. Sep;21(5):745-752. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35474016/

- Retrospective cohort study in patient prescribed Trikafta after lung transplantation. This study found Trikafta is rarely prescribed and further studies are needed in this population to assess.

Pilewski JM, et al. (2022). Update on Lung Transplantation for Cystic Fibrosis. Clinics in chest medicine, 43(4), 821–840. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36344083/

- Review article of lung transplantation for cystic fibrosis.

Marty PK, et al. (2022). Risk factors and outcomes of non-tuberculous mycobacteria infection in lung transplant recipients: A systematic review and meta-analysis. The Journal of heart and lung transplantation. S1053-2498(22)02170-2. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36334962/

- Systematic review and meta-analysis of NTM disease and isolation in LTR and their influence on mortality and CLAD. Eleven studies totaling 3,371 patients were eligible for inclusion, 10 of which underwent meta-analysis. NTM disease was associated with increased mortality (HR 2.69, 95% CI 1.70-4.26; I2 = 0%) and CLAD (HR 2.11, 95% CI 1.03-4.35; I2 = 44%). NTM isolation was not associated with mortality in pooled analysis or CLAD in 1 included study.

Shah P, et al. (2021). Cystic fibrosis foundation consensus statements for the care of cystic fibrosis lung transplant recipients. J Heart Lung Transplant. Jul;40(7):539-556. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34103223/

- Consensus statement to help transplant teams manage care of cystic fibrosis post-lung transplant patients.

Benden C, et al. (2021). CFTR Modulator Therapy and Its Impact on Lung Transplantation in Cystic Fibrosis. Pulm Ther. Dec;7(2):377-393. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34406641/

- Describe recent outcomes with modulator therapy, describe use of modulators in progressive advanced CF lung disease, and describe lung transplant related outcomes in patients with CF.
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Benninger LA, et al. (2021). CFTR modulator use in post lung transplant recipients. J Heart Lung Transplant. Dec;40(12):1498-1501. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34538541/

- Single center experience with the use of elexacaftor/tezacaftor/ivacaftor, Trikafta, in adult post-lung transplant recipients

Kapnadak SG, et al. (2020). Cystic Fibrosis Foundation consensus guidelines for the care of individuals with advanced cystic fibrosis lung disease. J Cyst Fibros. 19(3): 344-354. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32115388/

- Consensus guideline summarizing the definition and care of patients with advanced CF.

Hewer SL, et al. (2020). Intravenous versus oral antibiotics for eradication of Pseudomonas aeruginosa in cystic fibrosis (TORPEDO-CF): a randomised controlled trial. Lancet Respir Med. (10):975-986. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33007285/

- Multicentre, parallel group, open-label, randomized controlled trial in 72 cystic fibrosis that found that treatment with IV ceftazidime for 14 days did not yield better outcomes than 12 weeks of oral ciprofloxacin (both regimens in combination with 12 weeks of inhaled colistimethate).

Rey MM, et al. (2019). Cystic Fibrosis: Emerging Understanding and Therapies. Annu Rev Med. 70: 197-210. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30312551/

- Review article detailing updates in pharmacologic management of CF as well as non-pulmonary manifestations and management.

Middleton PG, et al. (2019). Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. N Engl J Med. 381:1809-1819. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31697873/

- Phase 3, double-blind, placebo-controlled trial to assess the CFTR modulator elexacaftor-tezacaftor-ivacaftor in CF patients at least 12 years of age. Treatment demonstrated statistically significant improvements in all endpoints compared to placebo, including the primary endpoint of FEV1 change from baseline at week 4.

King CS, et al. (2019). Critical care of the adult patient with cystic fibrosis. CHEST, 155(1): 202-214. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30077689/

- Review article encompassing the pharmacologic and non-pharmacologic care of critically ill patients with CF.

Cheng TZ, et al. (2019). Decreased antibiotic utilization after sinus surgery in cystic fibrosis patients with lung transplantation. Am J Rhinol Allergy. 33(4): 354-358. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30781973/

- Single center retrospective study of lung transplant recipients with CF who underwent endoscopic sinus surgery at least 1 year after transplant. Antibiotic use in the 6 months after surgery compared to the 6 months prior was significantly decreased, with no difference in other outcomes such as hospitalizations.

Launay M, et al. (2018). Posaconazole Tablets in Real-Life Lung Transplantation: Impact on Exposure, Drug-Drug Interactions, and Drug Management in Lung Transplant Patients, Including Those with Cystic Fibrosis. Antimicrob Agents Chemother. 62: e02061-17. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29311077/

- Prospective cohort study of lung transplant recipients, stratified by CF vs non-CF, compared to control non-transplant group. Posaconazole tablets resulted in therapeutic trough levels in all groups, however levels in CF lung transplant recipients were significantly lower. The authors also report the effect of posaconazole on immunosuppression drug levels and the effect of concomitant PPI use.

Snell G, et al. (2017). The evolution of lung transplantation for cystic fibrosis: a 2017 update. Journal of Cystic Fibrosis, 16(5):553-65. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/28711221

- Summary of lung transplant in cystic fibrosis including patient characteristics and overall survival post-transplantation.

Lowery EM, et al. (2017). Increased risk of PTLD in lung transplant recipients with cystic fibrosis. Journal of Cystic Fibrosis, 16(6):727-34. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/28456611

- Over 30,000 lung transplant recipients were included with 17% having a CF diagnosis. This group had greater incidence of PTLD in addition to higher EBV and CMV mismatches.

Stuckey L, et al. (2014). Mycophenolic acid pharmacokinetics in lung transplant recipients with cystic fibrosis. Ther Drug Monit. Apr;36(2):148-51. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/24232127/

- Evaluated mycophenolate exposure in cystic fibrosis patients, fount that lower MPA exposure existed in these patients compared to non-CF patients.

Ramsey BW, et al. (2011). A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. New England Journal of Medicine, 365(18):1663-72. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22047557

- Randomized, double-blind, placebo-controlled trial in CF patients with at least on G551D-CFTR mutation of ivacaftor for 48 weeks. Estimated mean change from baseline at 24 weeks in FEV1 was significantly greater in the ivacaftor group. Effect was maintained through week 48. There were fewer pulmonary exacerbations, higher respiratory symptoms domain scores, greater weight gain, and decreased sweat chloride.

6.8 Miscellaneous

6.8.1 Hypogammaglobulinemia

Lew, J., et al. (2021). Perceptions Around Lung Transplant-Associated Hypogammaglobulinemia. Journal of clinical immunology, 41(8), 1940–1942. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/34351551

- Letter to the editor discussing risk factors and clinical outcomes of hypogammaglobulinemia after lung transplant.

Petrov AA, et al. (2018). A prospective observational study of hypogammaglobulinemia in the first year after lung transplantation. Transplant Direct, 4(8):e372. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/30255132

- This study evaluated pre and posttransplant IgG levels and incidence of infection, rejection, antibiotic use, and immunosuppression use in lung transplant recipients. Of 133 patients, severe hypogammaglobulinemia (IgG <400 mg/dL) was highest at the time of transplant (32.4%) while at 3, 6, 9, and 12 months posttransplant the prevalence was 7.4%, 7.5%, 8.9%, and 6.3%, respectively. Additionally, severe hypogammaglobulinemia was associated with ≥2 pneumonias (P=0.0006) and increased number of antibiotic courses (P=0.003) when compared to other lung transplant recipients.

Lichvar AB, et al. (2018). Detrimental association of hypogammaglobulinemia with chronic lung allograft dysfunction and death is not mitigated by on-demand immunoglobulin G replacement after lung transplantation. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/30537897

- This retrospective single-center cohort study compared use of intravenous Immunoglobulin-G (IVIG) in lung transplant recipients with hypogammaglobulinemia (IgG <700 mg/dL, n=216)) to those with hypogammaglobulinemia but remained untreated (n=192) and those without hypogammaglobulinemia (n=76) up to 300 days post-transplant and found that hypogammaglobulinemia was independently associated with death (HR 2.44, 95% CI 1.34-4.47), with death significantly different between groups at 2 years (35% vs. 19% vs. 16%, respectively). A-grade cellular rejection (ACR) was significantly different at 5 years with a composite rejection standardization score (CRSS) of 0.5 vs. 0.4 vs. 0.3 between groups, respectively. Additionally, gram-negative pneumonias occurred more often in those who received IVIG (P=0.04).

Noell BC, et al. (2013). Effect of hypogammaglobulinemia on the incidence of community-acquired respiratory viral infections after lung transplant. Transplant Proc, 45(6):2371-4. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/23747186

- Single-center retrospective chart review evaluating occurrence of community-acquired respiratory viruses (CARVs) among patients with normal and hypogammaglobulinemia (defined as IgG <700 mg/dL) found that of 263 lung transplant recipients, incidence of CARV was 27% in patients with normal IgG titers versus 23.4% in patients with hypogammaglobulinemia (P=0.62).

Kawut SM, et al. (2005). Risk factors and outcomes of hypogammaglobulinemia after lung transplantation. Transplantation, 79(12):1723-6. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/15973175

- Single-center retrospective chart review evaluating quantitative total and subclass IgG levels found of 57 lung transplant recipients, 34 (60%) had IgG levels <700 mg/dL, of which 8 (14%) had severe hypogammaglobulinemia defined as IgG <400 mg/dL with females vs males (25% vs 0%, P=0.07). Additionally, emphysema and BOS were additional risk factors for severe hypogammaglobulinemia. Severe hypogammaglobulinemia was associated with increased risk of pneumonia (P=0.01) and worse survival (P=0.04).

Goldfarb NS, et al. (2001). Hypogammaglobulinemia in lung transplant recipients. Transplantation, 71(2):242-6. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/11213067

- Single-center retrospective chart review evaluating post-transplant humoral immune status survey including total immunoglobulin levels (IgG, IgM, IgA) and IgG subclasses (IgG1-4) found of 67 lung transplant recipients, 47 (70%) had IgG levels <600 mg/dL, of which 25 (37%) had IgG levels <400 mg/dL, and 22 (33%) had IgG levels 400-600 mg/dL. Infections were significantly more common in patients with IgG <400 mg/dL and more common in patients with IgG 400-600 mg/dL versus patients with normal IgG levels with infections including: number of pneumonias (P=0.0006), bacteremias (P=0.02), total bacterial infections (P=0.002), tissue-invasive cytomegalovirus (P=0.01), invasive aspergillosis (P=0.001), total fungal infections (P=0.001), and total infections (P=0.006). Additionally, survival was poorest in patients with IgG levels <400 mg/dL.

6.8.2 Hyperammonemia

Grazioli, A., et al. (2023). Treatment of hyperammonemia using in-line renal replacement and hyperosmolar therapies within an extracorporeal membrane oxygenation circuit. Perfusion, 38(1), 193–196. https://pubmed.ncbi.nlm.nih.gov/34320858/

- Treatment of hyperammonemia after lung transplant includes removal of ammonia which requires renal replacement modalities that can both rapidly remove ammonia from the plasma space and allow for continuous removal to prevent rebound accumulation from intracellular stores. Prevention of iatrogenic osmotic lowering is required to prevent worsening of cerebral edema. Herein, we describe use of sequential in-line renal replacement therapy using both iHD and continuous venovenous hemofiltration within an ECMO circuit in conjunction with higher sodium dialysate and 7.5% hypertonic saline to achieve these treatment goals.

Buzo, B. F, et al (2022). Hyperammonemia syndrome post-lung transplantation: Case series and systematic review of literature. Transplant infectious disease : an official journal of the Transplantation Society, e13940. Advance online publication. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36039822/

- Case series of seven hyperammonemia syndrome (HS) cases with literature review. All HS cases had positive airway samples for Mycoplasmataceae, neurologic abnormalities and high ammonia levels post-transplant. Mortality (57%) was similar to that published in previous cases. The literature review supports that HS is an early complication post-transplant, associated with Ureaplasma spp. and Mycoplasma hominis infections and of worse prognosis in patients presenting cerebral edema and seizures.

Kamel, A, et al. (2022). Hyperammonemia After Lung Transplantation: Systematic Review and a Mini Case Series. Transplant international : official journal of the European Society for Organ Transplantation, 35, 10433. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35620675/

- Systematic review delineates possible etiologies of hyperammonemia after lung transplantation and highlights successful strategies used to manage this complication

Chan, P, et al. (2021). Emergent Plasmapheresis for Hyperammonemia in a Re-do Double Lung Transplant Patient. The Annals of Thoracic Surgery, S0003-4975. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33421386/

- Case report a patient who experienced hyperammonemia secondary to shock liver post re-do double lung transplant. The patient's ammonia level was persistently > 250 ug/dL despite conventional therapy. Ammonia levels returned to baseline after initiation plasmapheresis but the patient unfortunately still passed away.

Roberts SC, et al. (2020). Impact of screening and Tteatment of ureaplasma spp on hyperammonemia syndrome in lung transplant recipients: A single center experience. Clin Infect Dis. Retrieved from: https://doi.org/10.1093/cid/ciaa1570

- Single center retrospective cohort study of lung transplant recipients who underwent Ureaplasma spp testing pre-transplant in donor and recipient. 8.3% of recipients and 13.3% of donors had positive screening tests. Patients with positive donor organs who received empiric therapy with levofloxacin and azithromycin did not develop hyperammonemia syndrome.

Leger RF, et al. (2020). Hyperammonemia post lung transplantation: A review. Clin Med Insights, Circ Respir Pulm Med. 14: 1-7. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33192115/

- Review article detailing the pathophysiology, diagnostics, and management of hyperammonemia in the lung transplant patient population.

Kwon M, et al. (2020). Extracorporeal Liver Support for the Treatment of Hyperammonemia After Lung Transplantation. Transplantation, 104(3): e75-76. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31385932/

- Case report of 2 patients with acute hyperammonemic encephalopathy after lung transplantation managed with an extracorporeal liver support system.

Matson KM, et al. (2019). Successful treatment of Ureaplasma-induced hyperammonemia syndrome post-lung transplant. Transpl Infect Dis. 21(1): e13022. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30403322/

- Case report of lung transplant recipient with hyperammonemia empirically treated with doxycycline in addition to ammonia-lowering therapies. The patient improved and Ureaplasma species later identified via PCR and BAL culture.

Emtiazjoo AM, et al. (2019). Alternative Therapeutic Approach for the Management of Symptomatic Hyperammonemia Syndrome after Lung Transplantation. J Heart Lung Transplant. 38(4): S326. Retrieved from: https://www.jhltonline.org/article/S1053-2498(19)30826-5/fulltext

- Single center retrospective study of lung transplant recipients with symptomatic hyperammonemia managed with two different formulas: Ammonul or Buphenyl. All patients improved with no recurrence, suggesting Buphenyl as an appropriate alternative to Ammonul.

Chen C, et al (2016). Hyperammonemia syndrome after lung transplantation: A single center experience. Transplantation, 100(3):678-84. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/26335916

- This retrospective cohort series of lung transplant recipients (n=807) who developed hyperammonemia syndrome, defined as symptoms of encephalopathy and plasma ammonia level >200 umol/L, occurred in 8 patients postoperatively with a median time to onset 9 days, median peak ammonia level 370 umol/L. All patients were treated with hemodialysis, 7 of 8 patients were also treated with bowel decontamination, and 5 of 8 patients were treated with nitrogen scavenging agents. 6 of 8 patients died.

Anwar S, et al (2014). Symptomatic hyperammonemia after lung transplanation: Lessons learnt. Hemodial Int. 18(1):185-91. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/23998793

- This case series of lung transplant recipients (n=3) who developed hyperammonemia early postoperatively reports aggressive ammonia reduction with early initiation of hemodialysis, prolonged daily intermittent hemodialysis, high dialysis dose, and overnight slow low-efficiency dialysis improves survival.

Lichtenstein GR, et al. (2000). Fatal hyperammonemia after orthotopic lung transplantation. Ann Intern Med. 15;132(4):283-7. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/10681283

- This retrospective cohort study evaluated the incidence of hyperammonemia in lung transplant recipients postoperatively. Of 145 lung transplant recipients, 6 developed hyperammonemia within 26 days of transplant. The 30 day post-transplantation mortality rate was 67% for patients with hyperammonemia versus those without (17%, P=0.01).

Development of major gastrointestinal complications (P=0.03) and use of total parenteral nutrition (P=0.045) were associated with the development of hyperammonemia.

Tuchman M, et al. (1997). Hepatic glutamine synthetase deficiency in fatal hyperammonemia after lung transplantation. Ann Intern Med. 127(6):446-9. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/9313001/

- This case report of two lung transplant recipients who developed fatal hyperammonemia following transplant determined that activity of hepatic glutamine synthetase was markedly reduced (in patient 1, 12% of the mean value in controls; in patient 2, 28% of the mean value in controls), with a concomitant reduction in amount of glutamine synthetase protein also observed.

6.8.3 Inhaled nitric oxide

Ghadimi, K., et al. (2022). Inhaled Pulmonary Vasodilator Therapy in Adult Lung Transplant: A Randomized Clinical Trial. JAMA surgery, 157(1), e215856. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34787647/

- Randomized blinded parallel-designed equivalence clinical trial to investigate whether the use of iEPO will lead to similar rates of severe/grade 3 primary graft dysfunction (PGD-3) after adult LT when compared with use of iNO. The primary outcome of PGD-3 development at 24, 48, or 72 hours after LT occurred in 46 of 103 patients (44.7%) in the iEPO group and 39 of 98 (39.8%) in the iNO group, leading to a risk difference of 4.9% (TOST 90% CI, -6.4% to 16.2%; P = .02 for equivalence). There were no significant between-group differences for secondary outcomes, including duration of mechanical ventilation, hospital and ICU lengths of stay, incidence and severity of acute kidney injury, postoperative tracheostomy placement, and in-hospital, 30-day, and 90-day mortality rates.

6.8.4 Donor derived cell free DNA

Keller M,et al. (2021). Use of donor-derived-cell-free DNA as a marker of early allograft injury in primary graft dysfunction (PGD) to predict the risk of chronic lung allograft dysfunction (CLAD). J Heart Lung Transplant. 2021 Jun;40(6):488-493. Retreived from: https://pubmed.ncbi.nlm.nih.gov/33814284/

- Prospective cohort study evaluated ddcfDNA measurements to PGD grades and comapred ddcfDNA measurements to those who developed CLAD. PGD patients developed high ddcfDNA early post-transplant and this was associated with CLAD.

Jang MK, et al. (2021). Donor-derived cell-free DNA accurately detects acute rejection in lung transplant patients, a multicenter cohort study. J Heart Lung Transplant. Aug;40(8):822-830. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34130911/

- Multicenter cohort study modering ddcfDNA in lung transplant patients to evaluate presence and acute rejection. Ths study found the ddcfDNA was a reliable measurement to detect acutre rejection.