6. Lung transplantation

6.1. Induction therapy

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.

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.

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.

- 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.

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.

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.

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.

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.

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.

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.

Allawadi 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.

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

Snell, G. I. 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.

6.2.1 Calcineurin inhibitors

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).

Calabrese, 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.

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.

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).

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.

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, Marquet P. (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 C,R 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.

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.

6.2.2 Cell cycle inhibitors

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.

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

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, Marquet P. (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.

6.2.3 Mammalian target of rapamycin inhibitors

Gottlieb J, et al (2018). 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.

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).

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, 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.

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.

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.

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.

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.

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

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.

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.

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

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

Parulekar A, Kao C (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

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.

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.

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

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

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.

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.

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.

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.

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.

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.

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.

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.

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.

6.4.3 Chronic lung allograft dysfunction

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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

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.

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)

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.

6.5 Retransplant/graft failure

6.5.1 General retransplant/graft failure

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

Bellier J, et al. (2019). Extracorpeal 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.

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.

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

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.

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 bronchiolitis obliterans syndrome

Pluchart H, et al. (2020). Restrictive allograft dysfunction after lung transplantation: is there a place for nintedanib?-a case report. Fundamental & Clinical Pharmacology 34.3 (2020): 408-411. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31755131/

- Case reportof a 63-year-old man who received a single right lung transplant who developed bronchiolitis obliterans syndrome which evolved into restrictive allograft disorder in 5 years. He was treated with nintedaninb 150 mg BID for 4 months without clinical benefit. The patient discontinued therapy due to GI intolerance.

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.

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.

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.

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.

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.

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.

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.

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.

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.

6.7 Lung diseases

6.7.1 Idiopathic pulmonary fibrosis

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.

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.

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

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

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.

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

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.

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.

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.

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.

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

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.

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.

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.

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.

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.

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.

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.

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.

6.7.3 Alpha-1 antitrypsin deficiency

Riley L, Loscano J (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).

Kleinervoa, 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, 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

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.

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

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).

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.

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.

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.

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.

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.

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.

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

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 $\geq$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

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.

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.

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.

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.

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.

- 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.

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.

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.