6. Lung transplantation

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6.1. Induction therapy

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

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

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

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

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. 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

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), 1527-1533. 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 and 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 CR et al. (2009). Tacrolimus and azathioprine versus cyclosporine and mycophenolate mofetil after lung transplantation: a retrospective cohort study. Journal of Heart and Lung Transplantation, 28(7), 697-703.
Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19560698

- Retrospective review of 120 lung transplant recipients maintained on either cyclosporine and mycophenolate (n = 37) or tacrolimus and azathioprine (n = 83) in

combination with prednisone and IL-2 receptor antagonist induction. Patients in the tacrolimus/azathioprine group had significantly better pulmonary function as measured by FEV1 and FVC at 12 months. No differences in acute rejection, BOS or survival were observed.

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

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

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

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 and 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

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 post-transplant. 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

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

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 peritransplant 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

6.4.1 Acute Cellular Rejection

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

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 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 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), E-published ahead of print. 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 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

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

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: long-term 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.

6.5.1 Primary Graft Dysfunction

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

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

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

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

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 5-year 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

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 at 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 at 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 at 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 at 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

Chen C, et al (2016). Hyperammonemia Syndrome After Lung Transplantation: A Single Center Experience. Transplantation, 100(3):678-84. Retrieved 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 at 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 transplanation. Ann Intern Med, 15;132(4):283-7. Retrieved at 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 posttransplantion 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.

- 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.