5. Heart transplantation

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5.1 Induction therapy

Truby LK, et al. (2020). Impact of Induction Immunosuppression on Post-Transplant Outcomes of Patients Bridged with Contemporary Left Ventricular Assist Devices. ASAIO J, 66(3):261-267. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Impact+of+Induction+Immunosuppression+on+Post-Transplant+Outcomes+of+Patients+Bridged+with+Contemporary+Left+Ventricular+Assist+Devices.

- Retrospective UNOS database review of patients who had a contemporary, durable, continuous-flow LVAD at the time of heart transplant. Propensity score matching was used to balance characteristics between those who did and did not receive induction therapy. There were no significant differences in graft survival, freedom from hospitalization for rejection, and freedom from hospitalization for infection. However, those who received induction therapy, particularly antithymocyte globulin, experienced a longer time to development of transplant coronary artery disease. Residual bias in patient selection may still exist in this study, but the results suggest that routine induction therapy in patients bridged to heart transplant with contemporary, durable, continuous-flow LVADs may be considered.

Amin AA, et al. (2019). Impact of Induction Immunosuppression on Patient Survival in Heart Transplant Recipients Treated with Tacrolimus and Mycophenolic Acid in the Current Allocation Era. Clin Transplant, 33 (8):e13651. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/31230375.

- Heart transplant recipients receiving combination TAC and MPA showed that neither rATG or IL2-RA was associated with survival benefit. Patients receiving rATG showed a significantly higher mortality than patients receiving IL2-RA. Patient receiving IL2-RA showed a trend toward higher associated mortality.

Starling RC, et al. (2019). Accelerated Allograft Vasculopathy With Rituximab After Cardiac Transplantation. J Am Coll Cardiol, 74(1):36-51. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/31272550

- This study randomized 163 patients to either rituximab 1,000 mg or placebo on days 0 and 12 post transplant to determine if there was a difference in development of CAV. Patients receiving rituximab had significantly higher percent atheroma volume at one year, with similar rates of rejection and mortality.

Gale SE, et al. (2019). Alemtuzumab Induction Versus Conventional Immunosuppression in Heart Transplant Recipients. Journal of Cardiovascular Pharmacology and Therapeutics, 24(5):435-441. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Alemtuzumab+Induction+Versus+Conventional+Immunosuppression+in+Heart+Transplant+Recipients.

- Retrospective single-center study comparing 26 patients who met criteria for induction and received alemtuzumab along with reduced tacrolimus, mycophenolate mofetil, and steroids to 26 patients who received standard immunosuppression without induction. At 12 months, alemtuzumab was associated with lower incidences of any rejection of any severity, ACR of any severity, and ACR of grade ≥2. No differences were seen in any rejection of grade ≥2 or AMR. Alemtuzumab was also associated with better preserved renal function in comparison to the group without induction. No differences were seen between groups in neutropenia requiring G-CSF or infections.

Jarmi T, et al. (2018). Outcomes of Induction Therapy with Rabbit Anti-Thymocyte Globulin in Heart Transplant Recipients: A Single Center Retrospective Cohort Study. Ann Transplant, 19 (23): 422-426. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29915167

- Induction with rATG added no additional survival benefit in heart transplant recipients. Patients not receiving induction therapy were found to have higher life expectancy at both 5 and 10 years post induction.

Briasoulis A, et al. (2018). Induction Immunosuppressive Therapy in Cardiac Transplantation: A Systematic Review and Meta-Analysis. Heart Fail Rev, 23 (5): 641-649. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29532201.

- Patients receiving induction therapy were found to have similar risk of moderate-to-severe rejection, all-cause death, infection, and cancer than patients that did not receive induction therapy. Patients receiving IL2-RA was associated with a significantly higher risk of moderate-to-severe rejection than patients receiving rATG with similar risk of death, infections, and cancer.

Kittipibul V, et al. (2017). Low-dose basiliximab induction therapy in heart transplantation. Clinical Transplantation, 31:e13132. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28990220.

- The utilization of low-dose de novo basiliximab for induction therapy in heart transplant recipients was shown to have favorable efficacy and safety outcomes. The use of calcineurin inhibitor (CNI) initiation in a low-risk population could be safely delayed using the strategy of modified low-dose post-operative basiliximab. Early corticosteroid wean was also found to be favorable with low-dose basiliximab use but with a higher CNI level and higher doses of mycophenolate.

Ruan V, et al. (2017). Use of Anti-Thymocyte Globulin for Induction Therapy in Cardiac Transplantation: A Review. Transplant Proc, 49(2):253-259. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28219580

- Use of Anti-thymocyte Globulin for induction therapy in cardiac transplant review article

Aliabadi AZ, et al. (2016). Impact of Rabbit Antithymocyte Globulin Dose on Long-term Outcomes in Heart Transplant Patients. Transplantation, 100(3):685-93. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Impact+of+Rabbit+Antithymocyte+Globulin+Dose+on+Long-term+Outcomes+in+Heart+Transplant+Patients.

- This retrospective data suggest that a cumulative rATG dose of 4.5 to 7.5 mg/kg for induction may offer a better risk-benefit ratio than lower or higher doses, with acceptable rates of infection and posttransplant malignancy. Prospective trials are needed.

Azarbal B, et al. (2016). Induction Therapy With Antithymocyte Globulin in Patients Undergoing Cardiac Transplantation Is Associated With Decreased Coronary Plaque Progression as Assessed by Intravascular Ultrasound. Circ Heart Fail, 9(1). Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Induction+Therapy+With+Antithymocyte+Globulin+in+Patients+Undergoing+Cardiac+Transplantation+Is+Associated+With+Decreased+Coronary+Plaque+Progression+as+Assessed+by+Intravascular+Ultrasound.

- Induction therapy with ATG is associated with reduced first-year coronary plaque progression as assessed by IVUS, despite an increased prevalence of sensitized patients with a trend toward more rejection.

Arman D, et al. (2016). Do Prior Driveline Infections Increase the Risk of Infection in Heart Transplant Patients Treated With Rabbit Antithymocyte Globulin Induction Therapy? Transplant Proc, 48(10):3393-3396. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27931587

- The use of ATG induction in patients with prior DLIs did not seem to increase the risk for posttransplant infection (eg, sternal wound infection). ATG induction can therefore be safely used in this population.

Ansari D, et al. (2015). Induction with anti-thymocyte globulin in heart transplantation is associated with better long-term survival compared with basiliximab. J Heart Lung Transplant, 34(10):1283-1291. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Induction+with+anti-thymocyte+globulin+in+heart+transplantation+is+associated+with+better+long-term+survival+compared+with+basiliximab

- A total of 9,324 transplantations performed between 2000 and 2011 whose recipients received ATG (n = 6,144) or BAS (n = 3,180). One-year survival was similar for both groups, 90% vs 91% (p = 0.858). However, use of BAS was associated with poorer long-term survival compared with ATG at 5 years (77% vs 82%, p = 0.005) and at 10 years (64% vs 67%, p = 0.007). In multivariable Cox model, use of BAS remained associated with increased mortality over a median follow-up of 3.0 years (range, 0-12 years), with a hazard ratio of 1.22 (95% confidence interval, 1.09-1.37; p < 0.001). The use of ATG rather than BAS as induction therapy appears to be associated with better long-term survival. A prospective study is necessary to confirm these findings.

Whitson BA, et al. (2015). Impact of induction immunosuppression on survival in heart transplant recipients: a contemporary analysis of agents. Clin Transplant, 29(1):9-17. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Impact+of+induction+immunosuppression+on+survival+in+heart+transplant+recipients%3A+a+contemporary+analysis+of+agents.

- In a contemporary analysis of heart transplant recipients, an overall analysis of induction agents does not appear to impact survival, as compared to no induction immunosuppression. While ALG/ATG/thymoglobulin appeared to have a beneficial effect on survival compared to IL-2Rab in the univariable model, this difference was no longer statistically significant once we adjusted for clinically relevant covariates.

Zuckermann A, et al. (2015). Thymoglobulin induction in heart transplantation: patient selection and implications for maintenance immunosuppression. Transpl Int, 28(3):259-69. Retrieved at: https://www.ncbi.nlm.nih.gov/pubmed/?term=Thymoglobulin+induction+in+heart+transplantation%3A+patient+selection+and+implications+for+maintenance+immunosuppression.

- Experts from Germany, Austria, and Switzerland convened to identify indications for rATG induction in heart transplantation and to develop an algorithm for its use based on patient characteristics.

Penninga L, et al. (2013). Immunosuppressive T-cell antibody induction for heart transplant recipients. Cochrane Database Systematic Reviews, 12: CD008842. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/24297433

- This review included 22 RCTs evaluating the use of antibody induction for heart transplant recipients. Acute rejection occurred less frequently with IL2-RA compared to no induction as well as with polyclonal antibody induction compared to IL2-RA and no significant differences regarding mortality, infection, or CAV, cancer or adverse events were detected. However, all included studies were thought to have a high risk of bias and no clear indication of benefit or harm associated with antibody induction could be demonstrated by this review.

Goland S, et al. (2008). Induction Therapy with Thymoglobulin After Heart Transplantation: Impact of Therapy Duration on Lymphocyte Depletion and Recovery, Rejection, and Cytomegalovirus Infection Rates. Journal of Heart and Lung Transplantation, 27: 1115-1121. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/18926403

- rATG induction consisting of 1.5 mg/kg doses given for five days was compared to a seven day course. Patients receiving the longer induction regimen experienced significantly less acute rejection (≥ 1B) at one year without an increase in CMV or bacterial infections.

Carrier M, et al. (2007). Basiliximab and rabbit anti-thymocyte globulin for prophylaxis of acute rejection after heart transplantation: a non-inferiority trial. Journal of Heart and Lung Transplantation, 26: 258-263. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/17346628

- Patients receiving rATG induction experienced less acute rejection at six months than those receiving basiliximab. Non-inferiority of basiliximab was not demonstrated in this investigation.

Mattei MF, et al. (2007). Lower risk of infectious deaths in cardiac transplant patients receiving basiliximab versus anti-thymocyte globulin as induction therapy. Journal of Heart and Lung Transplantation, 26: 693-699. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/17613399

- Prospective, randomized, multi-center comparison of basiliximab and rATG. The incidences of the composite safety end-point (serum sickness, fever, cutaneous rash, anaphylaxis, infection, thrombocytopenia, leukopenia and PTLS) and death due to infection were significantly less in the basiliximab group. No differences in the composite efficacy endpoint (death, graft loss, acute rejection > 1B, acute rejection associated with hemodynamic compromise or treated with antibody therapy, loss to follow up) were observed.

Lindenfeld J, et al (2004). Drug Therapy in the Heart Transplant Recipient Part I: Cardiac Rejection and Immunosuppressive Drugs. Circulation, 110: 3734-3740. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/15596559

- First article in a four-part series reviewing medication management for heart transplant recipients. This one focuses on rejection and induction agents.

Cantarovich M, et al. (2004). Antithymocyte globulin induction allows a prolonged delay in the initiation of cyclosporine in heart transplant patients with postoperative renal dysfunction. Transplantation, 78: 779-781. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/15371689

- Patients experiencing post-operative renal dysfunction received rATG induction with delayed initiation of cyclosporine. Compared to controls that received cyclosporine beginning on POD2, no significant differences in acute rejection or patient survival were observed.

5.2 Maintenance therapy

5.2.1 Calcineurin Inhibitors

Guethoff S, et al. (2013). Ten-year results of a randomized trial comparing tacrolimus versus cyclosporine a in combination with mycophenolate mofetil after heart transplantation. Transplantation, 95: 629-634. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23423270

- Freedom from acute rejection was significantly greater at 1, 5 and 10 years for patients receiving tacrolimus-based maintenance immunosuppression. Freedom from CAV was also increased for

the tacrolimus group compared to those receiving cyclosporine. No significant differences in patient survival at 1, 5, or 10 years were observed.

Patel JK, et al. (2007). Tacrolimus in heart transplant recipients: An overview. Biodrugs, 21:139-143. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/17516709

- Review of investigations comparing tacrolimus to cyclosporine for cardiac transplantation.

Grimm M, et al. (2006). Superior prevention of acute rejection by tacrolimus vs. cyclosporine in heart transplant recipients--a large European trial. American Journal of Transplantation, 6(6):1387-1397. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/16686762

- Incidence of BPAR ≥ 1B and 3A at six months was significantly decreased for patients receiving tacrolimus compared to cyclosporine. TAC-treated patients also developed significantly more NODAT, but less hyperlipidemia and HTN.

Kobashigawa JA, et al. (2006). Tacrolimus with mycophenolate mofetil (MMF) or sirolimus vs. cyclosporine with MMF in cardiac transplant patients: 1-year report. American Journal of Transplantation, 6:1377-1386. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/16686761

- No significant difference in the primary endpoint of grade 3A or greater rejection or rejection associated with hemodynamic compromise was detected. However, significant differences in any treated rejection, median serum creatinine and triglycerides occurred and favored the combination of tacrolimus and MMF.

5.2.2 Antiproliferatives

Woillard JB, et al. (2015). Mycophenolic mofetil optimized pharmacokinetic modelling, and exposure-effect associations in adult heart transplant recipients. Pharmacol Res, 99:308-15. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Mycophenolic+mofetil+optimized+pharmacokinetic+modelling%2C+and+exposure-effect+associations+in+adult+heart+transplant+recipients.

- MPA measured AUC adjusted on CNI exposure was significantly associated with rejection (per unit increase: HR [95% CI]=0.97 [0.95-0.99], p=0.0122), while no effect was shown for adverse events attributable to MMF. An AUC threshold of 50 mg×h/L was proposed (sensitivity=77%, specificity=25%) beyond which the risk of rejection was significantly increased (low vs. high: HR=3.48 [1.21-10.0], p=0.0204).

Eisen HJ, et al. (2005). Three-Year Results of a Randomized, Double-Blind, Controlled Trial of Mycophenolate Mofetil Versus Azathioprine in Cardiac Transplant Recipients. Journal of Heart and Lung Transplantation, 24:517-525. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/15896747

- Patients receiving AZA were retransplanted or died more frequently and had a shorter time to retransplantation or death than the MMF group. MMF-treated patients also had a smaller change in mean maximal intimal thickness compared to AZA (P = 0.056).

Kabashigawa J, et al. (2005). Review of Major Clinical Trials with Mycophenolate Mofetil in Cardiac Transplantation. Transplantation, 80:S235-S243. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/16251856

- Review summarizing MMF efficacy studies as well as use in pediatric heart transplantation, coronary allograft vasculopathy and therapeutic drug monitoring.

Kobashigawa J, et al. (1998). A randomized active-controlled trial of mycophenolate mofetil in heart transplant recipients. Transplantation, 66:507-515. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/9734496

- Rejection that required treatment as well as mortality at one year were significantly reduced in the MMF group. MMF-treated patients did experience more opportunistic infections, predominately HSV.

5.2.3 Corticosteroids

Elboudwarej O, et al. (2017). Corticosteroid wean after heart transplantation-Is there a risk for antibody formation? Clin Transplant, 31(4). Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28135788

- Few patients successfully weaned off prednisone after heart transplant develop de novo circulating antibodies but are not at increased risk for developing rejection.

5.2.4 Mammalian target of rapamycin (mTOR) inhibitors

Gustafsson F, et al. (2020). Everolimus Initiation With Early Calcineurin Inhibitor Withdrawal in De Novo Heart Transplant Recipients: Long-term Follow-up From the Randomized SCHEDULE Study. Transplantation, 104(1):154-164. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Everolimus+Initiation+With+Early+Calcineurin+Inhibitor+Withdrawal+in+De+Novo+Heart+Transplant+Recipients%3A+Long-term+Follow-up+From+the+Randomized+SCHEDULE+Study

- In the SCHEDULE trial, heart transplant recipients were randomized to everolimus with reduced-exposure calcineurin inhibitor to weeks 7-11 after transplant, followed by increased everolimus exposure with cyclosporine withdrawal or standard-exposure cyclosporine. After the core 12 month study, immunosuppression was according to the investigator's preference. At 5-7 years post-transplant, renal function continued to be better and CAV continued to be less common in the everolimus group. With regard to BPAR, while there were no events in the everolimus group between the year 3 visit and the 5-7 year visit and the difference between groups in BPAR from time of transplantation to the 5-7 year visit was not significant, there were more treated BPAR events in the everolimus group from time of transplantation to the 5-7 year visit. Graft dimensions and function were similar between groups.

Barten MJ, et al. (2019). Comparing everolimus-based immunosuppression with reduction or withdrawal of calcineurin inhibitor reduction from 6 months after heart transplantation: The randomized MANDELA study. Am J Transplant, 19:3006-3017.

- Heart transplant recipients were randomized at month 6 post-transplant to either convert to CNI-free immunosuppression with everolimus and MPA or to continue reduced-exposure CNI with concomitant everolimus. Target everolimus troughs were 5-10 ng/mL for both groups. The CNI-free regimen was associated with better renal function but more BPAR. Notably, 6 of 15 BPAR episodes in the CNI-free group occurred with everolimus concentration <5 ng/mL.

Saber-Moghaddam N, et al. (2019). The Change of Immunosuppressive Regimen from Calcineurin Inhibitors to Mammalian Target of Rapamycin (mTOR) Inhibitors and its Effects on Malignancy Following Heart Transplantation. Int Immunopharmacol, 69:150-158. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/30711744

- Patients converted from CNI to mTOR post-heart transplantation showed a reduction in the development of malignancy and an overall reduction in nephrotoxicity vs patients remaining on a CNI based regimen. The conversion to mTOR from CNI was found to be safe with an overall reduction in all-cause mortality.

Asleh R, et al. (2018). Long-Term Sirolimus for Primary Immunosuppression in Heart Transplant Recipients. J Am Coll Cardiol, 71(6):636-650. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29420960.

- Patients that were converted to sirolimus from CNI vs CNI alone experienced a significant attenuation in progression of cardiac allograft vasculopathy (CAV) and reduction in all-cause mortality. Patients also experienced a lower incidence of CAV related events when switched to sirolimus vs. CNI alone.

Hu YN, et al. (2017). High-Dose Calcineurin Inhibitor-Free Everolimus as a Maintenance Regimen for Heart Transplantation May be a Risk Factor for Pneumocystis Pneumonia. Transpl Infect Dis, 19(4). Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28425200

- In a retrospective review, heart transplant recipients receiving tacrolimus vs. conversion to tacrolimus were found to have non-significant differences in survival rate, rejection rate, and infections except for PJP. A total of 6 patients were diagnosed with PJP in the everolimus conversion group versus the 0 in the control group indicating a potential for higher incidence of PJP with everolimus conversion.

Nelson LM, et al. (2017). Effect of Calcineurin Inhibitor-Free, Everolimus-Based Immunosuppressive Regimen on Albuminuria and Glomerular Filtration Rate After Heart Transplantation. Transplantation, 101(11):2793-2800. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28230646.

- Patients receiving everolimus vs standard CNI immunosuppression were found to have a significantly higher eGFR at both 1 and 3 years' post-transplantation but a higher urine albumin/creatinine ratio (UACR) than those receiving standard CNI immunotherapy.

Simha V, et al. (2017). Sirolimus Therapy Is Associated with Elevation in Circulating PCSK9 Levels in Cardiac Transplant Patients. J Cardiovasc Transl Res, 10(1):9-15. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=10.1007%2Fs12265-016-9719-8

- Sirolimus used in transplantation is often associated with hypercholesterolemia. We measured serum lipid and PCSK9 levels in 51 heart transplant recipients who had their immunosuppressive therapy switched from calcineurin inhibitors to sirolimus. The switch resulted in a 23% increase in LDL cholesterol, and 46% increase in triglycerides and PCSK9 levels increased from 316 ± 105 ng/mL to 343 ± 107 ng/mL ($p = 0.04$), however the change in PCSK9 levels did not correlate with an increase in lipid levels ($p = 0.2$). To investigate the mechanism for the variability in the change in PCSK9 levels, lymphoblastoid cell lines were incubated with both sirolimus and everolimus, resulting in a 2-3 fold increase in PCSK9 expression and protein levels in mTOR inhibitor sensitive but not in mTOR inhibitor resistant cell lines. This first in human study demonstrates that sirolimus therapy is associated with elevation in PCSK9 levels which is not associated with sirolimus-induced hypercholesterolemia.

Van Keer J, et al. (2017). The CECARI Study: Everolimus (Certican®) Initiation and Calcineurin Inhibitor Withdrawal in Maintenance Heart Transplant Recipients with Renal Insufficiency: A Multicenter, Randomized Trial. J Transplant. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28316834

- Heart transplant recipients with baseline renal insufficiency randomized to start everolimus with CNI withdrawal or continuation of CNI did not show a significant change in measured glomerular filtration rate (mGFR) from baseline to year 3 post randomization. No difference was found between all-cause mortality, major cardiovascular events, or treated acute rejection between the two groups.

Andreassen AK, et al. (2016). Everolimus Initiation With Early Calcineurin Inhibitor Withdrawal in De Novo Heart Transplant Recipients: Three-Year Results From the Randomized SCHEDULE Study. Am J Transplant, 16(4):1238-47. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Everolimus+Initiation+With+Early+Calcineurin+Inhibitor+Withdrawal+in+De+Novo+Heart+Transplant+Recipients%3A+Three-Year+Results+From+the+Randomized+SCHEDULE+Study.

- In a randomized, open-label trial, de novo heart transplant recipients were randomized to everolimus with reduced-exposure calcineurin inhibitor to weeks 7-11 after transplant, followed by increased everolimus exposure with cyclosporine withdrawal or standard-exposure cyclosporine. Early CNI withdrawal after heart transplantation supported by everolimus, mycophenolic acid and steroids with lymphocyte-depleting induction was shown to be safe at intermediate follow-up. This regimen, used selectively, may offer adequate immunosuppressive potency with a sustained renal advantage, however, at the risk of increased biopsy proven acute rejection.

Mirza K, et al. (2016). Effect of everolimus initiation and early calcineurin inhibitor withdrawal on myocardial FOXP3+ regulatory T cells in heart transplantation. Transpl Immunol, 38:75-77. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Effect+of+everolimus+initiation+and+early+calcineurin+inhibitor+withdrawal+on+myocardial+FOXP3%2B+regulatory+T+cells+in+heart+transplantation.

- Everolimus treatment combined with early CNI elimination is associated with increased densities of Tregs 12-months post-HTx compared to patients receiving CNI based regimen. Furthermore, the density of myocardial FoxP3+ cells early after transplantation appears to predict at least one measure of CAV burden after one year.

Lesche D, et al. (2015). Influence of CYP3A5 genetic variation on everolimus maintenance dosing after cardiac transplantation. Clin Transplant, 29(12):1213-20. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Influence+of+CYP3A5+genetic+variation+on+everolimus+maintenance+dosing+after+cardiac+transplantation.

- Everolimus pharmacokinetics in HTx recipients is highly variable. This preliminary data on patients on a CNI-free therapy regimen suggest that CYP3A5 genetic variation may contribute to this variability.

Qiu Y, et al. (2015). Conversion From Calcineurin Inhibitors to Mammalian Target-of-Rapamycin Inhibitors in Heart Transplant Recipients: A Meta-Analysis of Randomized Controlled Trials. Transplant Proc, 47(10):2952-6. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Conversion+From+Calcineurin+Inhibitors+to+Mammalian+Target-of-Rapamycin+Inhibitors+in+Heart+Transplant+Recipients%3A+A+Meta-Analysis+of+Randomized+Controlled+Trials.

- Conversion from CNI to mTORi therapy may improve the renal function in HTRs, but the patients may suffer from a high incidence of mTORi-associated adverse events. Therefore, conversion to mTORi must be carefully assessed for the benefits and risks.

Fuchs U, et al. (2012). Efficacy and Safety of Low-Dose Everolimus as Maintenance Immunosuppression in Cardiac Transplant Recipients. Journal of Transplantation, Article ID 976921. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22577516

- Everolimus 0.75 mg BID targeting trough levels of 5-8 mcg/L was compared to 0.5 mg BID targeting levels of 3-5 mcg/L and no significant difference with respect to the primary composite endpoint including death, rejection, and discontinuation of everolimus was detected.

Topilsky Y, et al. (2012). Sirolimus as Primary Immunosuppression Attenuates Allograft Vasculopathy with Improved Late Survival and Decreased Cardiac Events After Cardiac Transplantation. Circulation, 125:708-720. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22207715

- Retrospective evaluation of converting CNI to sirolimus-based maintenance immunosuppression. Plaque index progression, vascular remodeling, freedom for cardiac events and patient survival were all improved with conversion to sirolimus.

Eisen HJ, et al. (2003). Everolimus for the Prevention of Allograft Rejection and Vasculopathy in Cardiac-Transplant Recipients. New England Journal of Medicine, 349: 847-858. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/12944570

- Randomized, double-blind comparison of 1.5 and 3 mg of everolimus and azathioprine in combination with cyclosporine and steroids. Patients receiving either everolimus dose experienced significantly less vasculopathy, composite efficacy endpoint (death, graft loss or retransplantation, loss to follow-up, biopsy-proven acute rejection of grade 3A, or rejection with hemodynamic compromise) and CMV infection.

5.2.5 Belatacept

Launay M, et al. (2019). Belatacept-based immunosuppression: A Calcineurin Inhibitor Sparing Regimen in Heart Transplant Recipients. Am J Transplant, 20(2):553-563. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/31452337

- Belatacept was initiated in the first three months after transplantation in 40 patients, including multiorgan transplant patients to preserve renal function. 76% of cases discontinued their CNI, and GFR improved within one month. 16 patients were discontinued due to GFR recovery (n = 4),

DSA no longer detectable (n = 1), compliance issues (n = 3), poor venous access (n = 2), multiple infections (n = 1), 1 death (fungal lung infection), and treatment failure (n = 4).

Ensor CR, et al. (2018). Belatacept for Maintenance Immunosuppression in Cardiothoracic Transplantation: The Potential Frontier. Clin Transplant, 32(10). Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/30058177

- This is a review article listing the potential benefits of belatacept utilization as maintenance immunosuppression in heart transplantation. Proposed benefits include cardiovascular, metabolic, and neurologic tolerability with lower utilization of calcineurin inhibitors which may prevent nephrotoxicity.

5.2.6 Other/General/Review Articles

Acquaro M, et al. (2020). Long-Term Effects of the Replacement of Calcineurin Inhibitors With Everolimus and Mycophenolate in Patients With Calcineurin Inhibitor-Related Nephrotoxicity. Transplantation Proceedings. [Epub ahead of print]. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Long-Term+Effects+of+the+Replacement+of+Calcineurin+Inhibitors+With+Everolimus+and+Mycophenolate+in+Patients+With+Calcineurin+Inhibitor%E2%80%93Related+Nephrotoxicity

- Retrospective observational study of 41 patients with renal impairment (eGFR <60 mL/min/1.73 m^2) for at least 3 months on CNI therapy who had CNI replaced with everolimus. Mean time from heart transplant at conversion was 12 years. Renal function tended to worsen prior to conversion of CNI to everolimus and tended to stabilize after conversion. While differences between patients who had improvement in renal function and patients who didn't were not significant, the group that saw improvement was characterized by less advanced age and a shorter time from heart transplant. One patient experienced acute late rejection and 3 patients developed chronic rejection.

Bürker BS, et al. (2017). Cognitive function after heart transplantation: Comparing everolimus-based and calcineurin inhibitor-based regimens. Clin Transplant, 31:4. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28185318

- Given the high prevalence of cognitive impairment in the sample, plus the known negative impact of cognitive impairment on clinical outcome, our results indicate that cognitive assessment should be an integrated part of routine clinical follow-up after HTx. However, everolimus- and CNI-based immunosuppressive regimens did not show differential impacts on cognitive function

Eisen HJ, et al. (2013). Everolimus Versus Mycophenolate Mofetil in Heart Transplantation: A Randomized, Multicenter Trial. American Journal of Transplantation, 13:1203–1216. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23433101

- Everolimus 1.5 mg and 3 mg daily plus steroids and cyclosporine targeting reduced trough concentration were compared to MMF plus steroids and traditional cyclosporine dosing with and without induction therapy. Patients receiving 3 mg of everolimus daily experienced increased mortality and this regimen was terminated. Everolimus was non-inferior to MMF with respect to the primary composite efficacy endpoint (biopsy-proven acute rejection, acute rejection associated with hemodynamic compromise, graft loss/retransplant, death or loss to follow-up) at 12 and 24 months. Mortality, primarily related to infection, at month 3 was higher when everolimus was combined with rATG induction, but was similar at 24 months.

Page, R. L. et al. (2005). Drug Therapy in the Heart Transplant Recipient Part IV: Drug–Drug Interactions. Circulation, 111:230-239. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/15657387

Lindenfeld J, et al. (2005). Drug Therapy in the Heart Transplant Recipient Part III: Common Medical Problems. Circulation, 111-117. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/15630040

Lindenfeld J, et al. (2004). Drug Therapy in the Heart Transplant Recipient Part II: Immunosuppressive Drugs. Circulation, 110:3858-3865. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/15611389

- These three complete the four-part series reviewing medication management for heart transplant recipients. Maintenance immunosuppression, drug-drug interactions and a variety of common

post-transplant disease states including hypertension, hyperlipidemia, coronary allograft vasculopathy, osteoporosis, diabetes and depression are discussed. The series is a bit dated, but provides a nice introduction for students and residents.

5.3 Desensitization therapy

Kransdorf EP, et al. (2017) Calculated panel-reactive antibody predicts outcomes on the heart transplant waiting list. J Heart Lung Transplant. 2017 Feb 17. pii: S1053-2498(17)31624-8. doi: 10.1016/j.healun.2017.02.015. [Epub ahead of print]. Retrieved from: www.ncbi.nlm.nih.gov/pubmed/28318744

- Sensitized heart transplant candidates are at high risk of adverse outcomes on the heart transplant waiting list. Clinicians should strive to minimize the CPRA by maximizing specificity in the selection of HLA antigens to exclude. The optimal clinical approach for candidates with high CPRA requires further study.

Eckman PM, et al. (2010). Immunosuppression in the sensitized heart transplant recipient. Current Opinion in Organ Transplantation, 15, 650–656. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/20689437

- This article reviews contemporary approaches to desensitization prior to and immunosuppression following heart transplant.

Patel J, et al. (2011). Reduction of alloantibodies via proteosome inhibition in cardiac transplantation. J Heart Lung Transplant, 30, 1320 – 6. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/21968130

- The first clinical experience using a plasma-cell-depleting strategy with bortezomib to reduce anti-HLA antibodies in the heart transplant population.

Kobashigawa JA, et al. (2011). The long-term outcome of treated sensitized patients who undergo heart transplantation. Clin Transplant, 25, E61–E67. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/20973825

- This study was done to determine whether reduction in circulating antibodies pre-transplant with plasmapheresis, intravenous gamma globulin and rituximab improves post-transplant outcomes.

Morrow WR, et al. (2012). Rapid Reduction in Donor-Specific Anti-Human Leukocyte Antigen Antibodies and Reversal of Antibody-Mediated Rejection With Bortezomib in Pediatric Heart Transplant Patients. Transplantation, 93, 319–324. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22179403

- This article documents the first use of bortezomib for cardiac transplant recipients in four pediatric heart recipients with biopsy-proven AMR, hemodynamic compromise, positive crossmatch, and high titer class I DSA.

Zeevi A, et al. (2012). HLA antibody profiling in thoracic transplantation undergoing desensitization therapy. Curr Opin Organ Transplant, 17, 416–422. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22790076

- This article reviews HLA antibody profiling pre-transplant and the effect of desensitization protocols on post-transplant outcomes.

Urban M, et al. (2012). Alloimmunosensitization in Left Ventricular Assist Device Recipients and Impact on Posttransplantation Outcome. ASAIO Journal, 58, 554–561. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23069898

- This article presents the current state of knowledge of possible immunologic mechanisms involved in alloimmunization of LVAD recipients, outlines new methods of antibody detection, compares various desensitization strategies, and presents an overview of clinical data assessing the impact of sensitization on post-transplantation outcome.

Chang D, et al. (2012). The use of the calculated panel reactive antibody and virtual crossmatch in heart transplantation. Curr Opin Organ Transplant, 17, 423–426. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22790077

- This article reviews the use of calculated panel reactive antibody and virtual crossmatch in heart transplant as well as current desensitization strategies.

Picascia A, et al. (2012). Current Concepts in Histocompatibility During Heart Transplant. Experimental and Clinical Transplantation, 3, 209-218. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22631055

- This article reviews strategies for detection of antibodies and current strategies for desensitization pre-transplant.

Kaufman, BD et al. (2011). Immunologic Considerations in Heart Transplantation for Congenital Heart Disease. Current Cardiology Reviews, 7, 67-71. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22548029

- This article reviews the causes of anti-HLA antibody production (allosensitization), preventive strategies for allosensitization before transplantation, treatment strategies for allosensitization before transplantation, consequences of HLA allosensitization after transplantation and treatment of HLA allosensitization and antibody-mediated rejection after transplantation.

Chih S, et al. (2016). Desensitization strategies in adult heart transplantation-Will persistence pay off? J Heart Lung Transplant, 35(8):962-72. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Desensitization+strategies+in+adult+heart+transplantation-Will+persistence+pay+off%3F

- Review article of desensitization strategies in adult heart transplantation. No approach has demonstrated significant and sustainable reductions in HLA antibody pre-transplant, and the ideal desensitization strategy remains elusive. In addition, clinical tools to evaluate the humoral response and efficacy of therapy are limited, focusing almost exclusively on HLA antibody detection. Importantly, desensitization is associated with significant costs and potential risks, and overall long-term outcomes and cost-effectiveness have not been sufficiently evaluated.

Geft D, et al. (2017). Current concepts for sensitized patients before transplantation. [Epub ahead of print]. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28306593

- The development of more accurate methods of detecting sensitization and defining the ideal desensitization strategies that can be more universally adopted and tested in clinical trials will serve to enlighten us and help many more highly sensitized patients not only make it to transplant, but also thrive posttransplant as well.

Nakamura et al. (2018). Successful Heart Transplantation After Desensitization in a Patient with Extremely High Panel-Reactive Antibody Levels and Pretransplant Donor-Specific Antibody: A Case Report. Transplant Proc, 50 (10): 4067-4070. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30577317.

- Case report describing the successful desensitization of a heart transplant recipient with severely elevated panel reactive antibody (PRA) and pre-transplant DSA positivity.

Shah et al. (2019). Desensitization in Heart Transplant Recipients: Who, When, and How. Clin Transplant, 33(8). Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/31206862.

- Review discussing status of antibody detection and identification, strength, and potential pathogenicity. Therapies such as mechanical removal of antibodies, IVIG, and novel immunosuppressive agents will be discussed.

Edwards et al. (2019). Impact and Predictors of Positive Response to Desensitization in Pediatric Heart Transplant Candidates. J Heart Lung Transplant, 38 (11):1206-1213. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/31672220.

- Patients were categorized as sensitized receiving desensitization, sensitized and not receiving desensitization, or non-sensitized. Desensitization response was found in 8 patients upon repeat

PRA testing after administration of IVIG. Factors such as ventricular assist device (VAD) and homograft combination were found to cause higher sensitization than either of the two alone. Patients undergoing sensitization therapy were associated with an increased likelihood of remaining listed longer and a longer time on the waitlist without impact on the rate of transplantation, mortality, or post-transplantation outcomes.

5.4 Rejection Management

5.4.1 Rejection - General

Poglajen G, et al. (2017). Low Serum Testosterone is Associated With Graft Function Early After Heart Transplantation. Clin Transplant. [Epub ahead of print]. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28314079

- Low serum testosterone levels appear to be associated with impaired graft function and an increased incidence of low-grade rejection episodes early after heart transplantation.

Savignano C, et al. (2017). Extracorporeal Photochemotherapy in Heart Transplant Rejection: A Single-Center Experience. Transfus Apher Sci, 56 (4): 520-524. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28774825.

- This is a retrospective analysis of heart transplant recipients receiving maintenance immunosuppression and extracorporeal photochemotherapy (ECP) for the treatment of rejection. Patients received ECP for recurrent rejection, persistent rejection, and mixed rejection with hemodynamic compromise. Patients receiving ECP had a low response rate (37.5%) when added to maintenance immunotherapy likely due to patient selection. Larger clinical trials are needed to determine the utility of ECP in heart rejection treatment or prophylaxis.

Kfoury AG, et al. (2016). Mixed cellular and antibody-mediated rejection in heart transplantation: In-depth pathologic and clinical observations. J Heart Lung Transplant, 35(3):335-41. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Mixed+cellular+and+antibody-mediated+rejection+in+heart+transplantation%3A+In-depth+pathologic+and+clinical+observations.

- Mixed rejection is not common, usually occurs early after transplant, and is associated with worse outcomes. Mixed rejection reflects a complex interplay between cellular and humoral processes, which varies with rejection severity.

Patel J, et al. (2015). Extracorporeal photopheresis in heart transplant rejection. Transfus Apher Sci, 52(2):167-70. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/25748232.

- Extracorporeal photopheresis (ECP) appears particularly useful in the management of select heart transplant recipients at risk of rejection, with recurrent rejection, or rejection associated with hemodynamic compromise. This summarizes the current clinical experience of ECP in heart transplantation.

Imamura T, et al. (2013). Successful Treatment of Hemodynamic Compromise Caused by Antibody-Mediated and Cellular Rejection in a Recipient 12 years After Heart Transplantation. Int Heart J, 54, 328-331. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/24097224

- This is a case report of successful treatment of rejection with repeated plasma exchange accompanied by a single administration of rituximab. The case of rejection was refractory to repeated steroid pulse treatment, intravenous immunoglobulin administration and intensifying immunosuppression.

Patel JK, et al. (2011). Cardiac allograft rejection. The Surgeon, 9, 160-167. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/21550522

- This article is a review of the current status of the diagnosis of cardiac allograft rejection as determined by the traditional endomyocardial biopsy, the more recent advances in the non-invasive evaluation of rejection, detection of circulating antibodies and the treatment of rejection.

Patel JK, et al. (2004). Immunosuppression, Diagnosis, and Treatment of Cardiac Allograft Rejection. Semin Thorac Cardiovasc Surg, 16:378-385. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/15635544

- This is a review article that addresses immunosuppression post-transplant as well as the diagnosis and treatment of cardiac allograft rejection.

5.4.2 Acute Cellular Mediated Rejection

Mateo R, et al. (2015). Relationship Between Hyperglycemia and Heart Transplant Rejection. Transplant Proc,47(9):2727-31. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/26680082

- Grade ≤1R rejection on biopsy was observed in 116 patients and grade ≥2R rejection (grade requiring increased anti-rejection treatment) in 41 patients. Although no significant differences in the preoperative fasting or inpatient mean glucose levels were found, the mean glucose levels from discharge to 1 year trended higher in those with grade ≥2R compared to grade ≤1R (128.8 ± 40.9 versus 142.2 ± 46.6 mg/dL, P = .084).

Ankersmit HJ, et al. (2003). Rapamycin as Rescue Therapy in a Patient Supported by Biventricular Assist Device to Heart Transplantation With Consecutive Ongoing Rejection. American Journal of Transplantation, 3, 231—234. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/12603219

- This is a case report of cardiac allograft rejection despite treatment with anti-thymocyte globulin (ATG), FK506, a mycophenolate switch and courses of multiple apheresis that was successfully treated with Rapamycin.

Lehrer MS, et al. (2001). Successful Reversal of Severe Refractory Cardiac Allograft Rejection by Photopheresis. J Heart Lung Transplant, 20:1233–1236. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/11704486

- This is a case report of 4 patients with refractory International Society of Heart and Lung Transplantation Grades IIIA to IV cardiac allograft rejection treated successfully with extracorporeal photopheresis.

5.4.3 Acute Antibody Mediated Rejection

Erdogan I, et al. (2018). Rituximab Therapy for Rejection in Pediatric Heart Transplant. Exp Clin Transplant, 16 (2): 199-203. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27210774.

- Case series of seven pediatric heart transplant patients were treated with plasma exchange (PLEX) and rituximab for antibody-mediated rejection post-heart transplantation. Overall, 5 patients experienced refractory persistent rejection required repeat doses of rituximab. A total of 4 patients died after diagnosis of AMR but not related to complications or adverse effects from rituximab.

Clerkin KJ, et al. (2017). Donor-specific anti-HLA antibodies with antibody-mediated rejection and long-term outcomes following heart transplantation. J Heart Lung Transplant. [Epub ahead of print]. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27916323

- DSA were inadequate to diagnose pAMR. Class II DSA provided prognostic information regarding future pAMR, graft dysfunction with pAMR, and graft loss.

Loupy A, et al. (2017). Gene Expression Profiling for the Identification and Classification of Antibody-Mediated Heart Rejection. Circulation, 135 (10): 917-935. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28148598.

- This prospective study aimed to asses endomyocardial biopsies to detect antibody-mediated rejection (AMR) across 4 transplant centers. Patients experiencing AMR showed a distinct pattern of injury characterized with inflammatory markers including monocytes/macrophages and natural killer cells directly correlating to the degree of injury and disease activity. This study demonstrates the potential utility of tissue based analysis for patients' experiencing AMR.

Manfredini V, et al. (2017). Antibody-mediated rejection in heart transplantation: new developments and old uncertainties. Curr Opin Organ Transplant. [Epub ahead of print]. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28301387

- Despite improvements in the diagnostic process, therapeutic strategies made little progress in addition to the consolidation of practices supported by limited evidence. Novel complement inhibitors appear promising in changing this scenario. Nevertheless, collaborative multicenter studies are needed to develop standardized approaches tailored to the highly variable clinical and laboratory features of AMR.

Tran A, et al. (2016). Donor-specific HLA alloantibodies: Impact on cardiac allograft vasculopathy, rejection, and survival after pediatric heart transplantation. J Heart Lung Transplant, 5(1):87-91. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Donor-specific+HLA+alloantibodies%3A+Impact+on+cardiac+allograft+vasculopathy%2C+rejection%2C+and+survival+after+pediatric+heart+transplantation

- Of the 105 patients, 45 (43%) developed de novo DSA. DSA-positive patients had significantly higher rates of coronary artery vasculopathy (CAV) compared with DSA-negative patients (36% vs 13%). The 5-year graft survival rate was 72.4% for DSA-negative patients and 21% for DSA-positive patients (< 0.001). De novo DSA has a strong negative impact on CAV, rejection, and graft survival in pediatric recipients of heart transplants.

Coutance G, et al. (2015). Late antibody-mediated rejection after heart transplantation: Mortality, graft function, and fulminant cardiac allograft vasculopathy. J Heart Lung Transplant, 34(8):1050-7. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Late+antibody-mediated+rejection+after+heart+transplantation%3A+Mortality%2C+graft+function%2C+and+fulminant+cardiac+allograft+vasculopathy.

- Prognosis after late AMR is poor despite aggressive immunosuppressive therapies. Fulminant CAV is a common condition in these patients. Microvascular inflammation is frequent in endomyocardial biopsy specimens before manifestation of symptomatic AMR.

Gazdic T, et al. (2015). Bortezomib-containing regimen for primary treatment of early antibody-mediated cardiac allograft rejection: a case report. Prog Transplant, 25(2):147-52. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Bortezomib-containing+regimen+for+primary+treatment+of+early+antibody-mediated+cardiac+allograft+rejection%3A+a+case+report.

- Primary treatment with a bortezomib-containing regimen appears to be a new therapeutic option for severe antibody-mediated rejection in heart transplant recipients.

Kaczorowski DJ, et al. (2013). Profound hyperacute cardiac allograft rejection rescue with biventricular mechanical circulatory support and plasmapheresis, intravenous immunoglobulin, and rituximab therapy. Journal of Cardiothoracic Surgery, 8:48. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/23497431

- This is a case report of hyperacute rejection managed with ventricular assist devices (VADs) for biventricular support during treatment with rituximab, intravenous immunoglobulin (IVIG), and plasmapheresis.

Chih S, et al. (2013). A Survey of Current Practice for Antibody Rejection in Heart Transplantation. American Journal of Transplantation, 13:1069–1074. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23414257

- This article reviewed and analyzed online survey data from 184 ISHLT members from medium to large volume adult transplant centers in North America and Europe to determine their practices regarding criteria for initiating treatment for rejection and the treatment of antibody mediated rejection.

Aggarwal A, et al. (2012). Low-Dose Rituximab Therapy for Antibody-Mediated Rejection in a Highly Sensitized Heart-Transplant Recipient. Tex Heart Inst J, 39(6):901-5. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23304051

- This is a case report regarding the role of low-dose rituximab as therapy for antibody-mediated rejection in heart-transplant patients.

Nair N, et al. (2011). Current and future challenges in therapy for antibody-mediated rejection. J Heart Lung Transplant, 30, 612–7. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/21474341

- This article discusses the challenges in treating antibody mediated rejection and provides a critical analysis of current and possible future therapies.

Jhang J, et al. (2007). Therapeutic Plasma Exchange Performed in Parallel with Extra Corporeal Membrane Oxygenation for Antibody Mediated Rejection after Heart Transplantation. Journal of Clinical Apheresis, 22, 333–338. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/18080271

- This is a case report demonstrating the use of therapeutic plasmapheresis in parallel with extracorporeal membrane oxygenation to alleviate antibody mediated rejection.

Kaczmarek I, et al. (2007). Successful Management of Antibody-Mediated Cardiac Allograft Rejection With Combined Immunoadsorption and Anti-CD20 Monoclonal Antibody Treatment: Case Report and Literature Review. J Heart Lung Transplant, 26, 511–5. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/17449422

- This is a case report of a patient with antibody mediated rejection who was successfully treated with 3 cycles of immunoadsorption and a single-dose administration of rituximab.

Garrett Jr. EH, et al. (2005). Treatment of Vascular Rejection With Rituximab in Cardiac Transplantation. J Heart Lung Transplant, 24, 1337–42. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/16143254

- This is a case report of 8 patients with antibody mediated rejection successfully treated with rituximab at a dose of 375 mg/m2 per week for 4 weeks.

Baran, DA et al. (2004). Refractory Humoral Cardiac Allograft Rejection Successfully Treated With a Single Dose of Rituximab. Transplantation Proceedings, 36, 3164–3166. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/15686719

- This is a case report of refractory humoral cardiac rejection successfully treated with a single dose of rituximab 375 mg/m2.

Aranda JM, et al. (2002). Anti-CD20 Monoclonal Antibody (Rituximab) Therapy for Acute Cardiac Humoral Rejection: A Case Report. Transplantation, 73:6, 907–910. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/11923690

- This is a case report of humoral rejection resistant to steroids, cyclophosphamide, and plasmapheresis successfully treated with rituximab.

Grauhan O, et al. (2001). Plasmapheresis and Cyclophosphamide in the Treatment of Humoral Rejection After Heart Transplantation. J Heart Lung Transplant, 20:316–321. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/11257558

- This is a retrospective study evaluating the use of corticosteroids and cytolytic antibodies vs. corticosteroids, cytolytic antibodies, and plasmapheresis to treat humoral rejection post heart transplant.

5.4.4 Rejection Surveillance

Agbor-Enoh S, et al. (2017). Applying Rigor and Reproducibility Standards to Assay Donor-Derived Cell-Free DNA as a Non-Invasive Method for Detection of Acute Rejection and Graft Injury After Heart Transplantation. J Heart Lung Transplant, 36 (9): 1004-1012. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28624139.

- Quantitative genomic techniques such as donor-derived cell-free DNA (%ddcfDNA) assays were found to be precise and reproducible across multiple laboratories and able to detect both cellular and antibody mediated rejection. Larger studies utilizing this technique are needed to determine the exact clinical utility of %ddcfDNA as an acute marker for episodes of cellular or acute antibody mediated rejection.

5.5 Graft Failure/Primary Graft Dysfunction (PGD)

Peled Y, et al. (2020). Preoperative statin therapy and heart transplantation outcomes. Annals Thorac Surg. [Epub ahead of print]. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/32156588

- Retrospective cohort study comparing PGD incidence between heart transplant recipients who were on statin therapy during the month prior to and at the time of transplantation (n=167) and those who were not (n=108)
- PGD was significantly lower among heart transplant recipients who received statin therapy prior to and at the time of heart transplantation (21 vs 60%, p<0.001).

Jennings DL, et al. (2017). Pre-cardiac transplant amiodarone use is not associated with postoperative mortality: An updated meta-analysis. Int J Cardiol. [Epub ahead of print]. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28238350

- Meta-analysis of the available evidence suggests that pre-operative amiodarone exposure does not increase mortality in cardiac transplant recipients.

Sabatino M, et al. (2017). Clinical relevance of the International Society for Heart and Lung Transplantation consensus classification of primary graft dysfunction after heart transplantation: Epidemiology, risk factors, and outcomes. J Heart Lung Transplant. [Epub ahead of print]. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28302502

- Consensus-defined P-GD identifies patients at major risk for early death and graft loss after HT, although the "mild" grade appeared under-represented and clinically irrelevant. The amplified negative effect of donor and recipient factors on P-GD risk underscores the need for appropriate donor-recipient match

Lushaj EB, et al. (2016). To use or not to use? Amiodarone before heart transplantation. Surgery. [Epub ahead of print]. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27876282

- Amiodarone use did not affect the incidence of atrial fibrillation nor 30-day and 1-year survival post-transplantation. Nevertheless, post-transplant pulmonary complications were significantly greater and 5-year survival was less among patients treated with amiodarone prior to transplant

Foster BJ, et al. (2015). High Risk of Graft Failure in Emerging Adult Heart Transplant Recipients. Am J Transplant, 15(12):3185-93. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/26189336.

- Crude age-specific graft failure rates were highest in 21-24 year olds (4.2 per 100 person-years). Compared to individuals with the same time since transplant, 21-24 year olds had significantly higher failure rates than all other age periods except 17-20 years (HR 0.92 [95%CI 0.77, 1.09]) and 25-29 years (0.86 [0.73, 1.03]). Among young first heart transplant recipients, graft failure risks are highest in the period from 17 to 29 years of age.

Morris AA, et al. (2015). Race and ethnic differences in the epidemiology and risk factors for graft failure after heart transplantation. J Heart Lung Transplant, 34(6):825-31. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/25682551

- Black HT recipients have the highest risk of GF, with immunologic factors conferring the greatest proportion of that risk. Racial differences in risk factors for GF after HT require further study.

5.6 Retransplantation

Tjang TS, et al. (2008). Tenderich G, Hornik L, Korfer R. Cardiac retransplantation in adults: an evidence-based systematic review. Thorac Cardiov Surg, 2008; 56:323-327. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/18704853

- A systematic review of 22 published studies regarding cardiac retransplantation in adults

Johnson MR, et al. (2007) Heart retransplantation. Am J Transplant, 7:2075-2081. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/17640316

- A review article in which a working group developed recommendations, based on available data and expert opinion, concerning heart retransplantation.
- Summarized all relevant trials of retransplantation in adults and pediatrics
- One-, three-, and five-year unadjusted graft survival was lower in retransplants than in first transplants (82% vs. 86%, 70% vs. 80%, & 58% vs. 73%, p<0.0001, respectively).

5.7 Heart Failure Etiologies and Management

5.7.1 Cardiomyopathy

5.7.1.1 Dilated Cardiomyopathy

Kaya MG, et al. (2014). Evaluation of beta-blockers on left ventricular dyssynchrony and reverse remodeling in idiopathic dilated cardiomyopathy: A randomized trial of carvedilol and metoprolol. Cardiology Journal, 21(4):434-41.1. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/24142686

- Carvedilol was associated with greater reduction in LVEDV, increase in LVEF and improvement in inter-ventricular dyssynchrony compared to metoprolol. Both medications improved intraventricular dyssynchrony, reverse remodeling and BNP levels.

Braun M, et al. (2009). The calcium channel blocker felodipine attenuates the positive hemodynamic effects of the beta-blocker metoprolol in severe dilated cardiomyopathy--a prospective, randomized, double-blind and placebo-controlled study with invasive hemodynamic assessment. International Journal of Cardiology, 32, 248-256. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/18579230

- Patients receiving metoprolol experienced significantly improved LVEF, LVEDD as well as decreased PAP and PCWP. When combined with felodipine these benefits were negated.

5.7.1.2 Restrictive Cardiomyopathy

Sousa M, et al. (2017). 1, Monohan G1, Rajagopalan N1, Grigorian A1, Guglin M2. Heart transplantation in cardiac amyloidosis. Heart Fail Rev, 22(3):317-27.. 2017 Mar 9. doi: 10.1007/s10741-017-9601-z. [Epub ahead of print] Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28281017

- Cardiac amyloidosis and heart transplantation review article

Rosenbaum AN, Edwards BS. (2015) Current indications, strategies, and outcomes with cardiac transplantation for cardiac amyloidosis and sarcoidosis. Curr Opin Organ Transplant. 2015 Oct;20(5):584-92. doi:10.1097/MOT.0000000000000229. Retrieved at: https://www.ncbi.nlm.nih.gov/pubmed/?term=Current+indications%2C+strategies%2C+and+outcomes+with+cardiac+transplantation+for+cardiac+amyloidosis+and+sarcoidosis.

- Outcomes after heart transplantation are typically worse than in patients undergoing heart transplantation for nonamyloid disease. This review analyzes the indications, strategies and outcomes in patients with amyloidosis and sarcoidosis.

5.7.1.3 Infectious Cardiomyopathy

Benatti RD, et al. (2017).1, Oliveira GH2, Bacal F3. Heart Transplantation for Chagas Cardiomyopathy .J Heart Lung Transplant. 36(6):597-603. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28284779

- Chagas cardiomyopathy (CC) and heart transplantation review article

5.7.1.4 Peripartum Cardiomyopathy

Westhoff-Bleck, M. et al (2013). Cardiovascular Disorders in Pregnancy: Diagnosis and Management. Best Practice & Research Clinical Obstetrics and Gynaecology, 27, 821-834. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23932772

- Summary of pathophysiology, diagnosis and treatment of cardiovascular disorders during pregnancy, including peri-partum cardiomyopathy.

Lund, LH, et al (2011). Myocardial recovery in peri-partum cardiomyopathy after continuous flow left ventricular assist device. Journal of Cardiothoracic Surgery, 6: 150. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22082339

- Case report of peri-partum cardiomyopathy requiring LVAD that recovered and remains stable in NYHA class I-II 18 months post-explantation.

Rasmusson, KD (2007). Long-term Outcomes of Cardiac Transplantation for Peri-partum Cardiomyopathy: A Multiinstitutional Analysis. Journal of Heart and Lung Transplantation, 26, 1097-1104. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/18022074

- Sixty-nine women who received a heart transplant for peri-partum cardiomyopathy (PPCM) were compared to males as well as females with and without history of pregnancy. Risk of rejection was greater for the PPCM group compared to males and females without previous pregnancy. Long-term survival for PPCM recipients was comparable to males and improved compared to other females.

5.7.1.5 Right Ventricular Cardiomyopathy

Ermakov S, et al. (2014). Combination drug therapy for patients with intractable ventricular tachycardia associated with right ventricular cardiomyopathy. Pacing and Clinical Electrophysiology, 37, 90-94. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/24102153

- Review of four RV cardiomyopathy cases with RV-originating ventricular arrhythmia refractory to monotherapy and/or ablation. Combination therapy with sotalol, flecainide and mexiletine was used to control arrhythmia.

5.7.2 Congenital heart disease

VanderPluym, C et al. (2013). Advanced Therapies for Congenital Heart Disease: Ventricular Assist Devices and Heart Transplantation. Canadian Journal of Cardiology, 29, 796-802. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23683470

- This article reviews reasons for VAD implantation in congenital heart disease (CHD), VAD support in Fontan circulation, challenges with human leukocyte antigen sensitization in heart transplantation (HT), and the effect of VAD support on HT in CHD.

Pincott, SE et al. (2011). Indications for Heart Transplantation in Congenital Heart Disease. Current Cardiology Reviews, 7, 51-58. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/22548027

- This article reviews the indications for transplantation in congenital heart disease, the timing of transplantation, as well as potential complications of transplantation in congenital heart disease.

McGlothlin, D et al. (2011). Transplantation in Adults With Congenital Heart Disease. Progress in Cardiovascular Diseases, 53, 312–323. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/21295673

- This article addresses some of the unique challenges to transplantation and post-transplant management in congenital heart disease.

Hosseinpour, A et al. (2006). Transplantation for adults with congenital heart disease. European Journal of Cardio-thoracic Surgery, 30, 508—514. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/16857376

- This article reviews indications for transplantation in congenital heart disease and addresses unique considerations and complications to transplant.

5.7.3 Valvular heart disease

Nishimura RA, et al. (2017). AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease. Circulation, 135: e1159–e1195. Retrieved from: https://www.ahajournals.org/doi/full/10.1161/CIR.0000000000000503

- Guidelines published by American College of Cardiology (ACC) and the American Heart Association (AHA) on treatment of patients with heart valve disorders, such as evaluation of patients with heart murmurs, prevention and treatment of endocarditis, management of valve disease in pregnancy, and treatment of patients with concomitant coronary artery disease (CAD), as well as more specialized issues that pertain to specific valve lesions.

Baumgartner H, et al. (2017). ESC/EACTS Guidelines for the management of valvular heart disease. *European Heart Journal*, 38(36): 2739–91. Retrieved from: https://academic.oup.com/eurheartj/article/38/36/2739/4095039

- Guidelines published by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) on management of valvular heart disease

5.7.4 LVAD pre-transplant

Miller RJH, et al. (2020) Transplant Outcomes in Destination Therapy Left Ventricular Assist Device Patients. ASAIO. 2020 Apr; 66(4):394-8. doi: 10.1097/MAT.0000000000001016. Retrieved at: https://www.ncbi.nlm.nih.gov/pubmed/31192848

- There was no significant difference in 1-year survival or survival time between heart transplant recipients who had LVADs implanted as bridge-to-transplant (BTT) versus destination therapy (DT) prior to transplantation. Post-transplantation non-fatal adverse events were also similar between both treatment groups.

Truby LK, et al. (2020) Impact of Induction Immunosuppression on Post-Transplant Outcomes of Patients Bridged with Contemporary Left Ventricular Assist Devices. ASAIO. 2020 Mar; 66(3):261-7. doi: 10.1097/MAT.0000000000001119. Retrieved at: https://www.ncbi.nlm.nih.gov/pubmed/32101996

- There was no significant difference in the primary outcomes of graft survival, freedom from hospitalization for rejection, and freedom from hospitalization for infection between BTT LVAD patients who received induction therapy (IT) and those who did not. There was also no significant difference in freedom from hospitalization for infection among transplant recipients who had an infected LVAD prior to transplantation. LVAD patients who received IT had increased freedom from transplant coronary artery disease (TCAD), with increased freedom from TCAD among those who received antithymocyte globulin compared to basiliximab.

Grimm JC, et al. (2016) Duration of Left Ventricular Assist Device Support Does Not Impact Survival After US Heart Transplantation. Ann Thorac Surg. 2016; 102(4):1206-12. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27319984

- In the largest, non-industry sponsored study of a modern bridge to transplant cohort, this study demonstrated that duration of LVAD support before orthotopic heart transplantation does not influence posttransplant morbidity or mortality. In subanalysis, support for 90 days or more is associated with improvements in pretransplant functional performance.

Healy AH, et al. (2016) Predictors of 30-day post-transplant mortality in patients bridged to transplantation with continuous-flow left ventricular assist devices--An analysis of the International Society for Heart and Lung Transplantation Transplant Registry. J Heart Lung Transplant. 2016 Jan;35(1):34-9. doi: 10.1016/j.healun.2015.07.007.Epub 2015 Jul 29. Retrieved at: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/26296960/

- In patients supported with continuous flow LVADs, risk factors for early mortality can be identified before transplant, including ventilator support, female recipient/male donor, increasing recipient age, and body mass index. Despite the inherent complexities of a reoperative surgery, patients bridged to transplant with CF LVADs have excellent peri-operative survival.

Ko BS, et al. (2016) Immunologic effects of continuous-flow left ventricular assist devices before and after heart transplant. J Heart Lung Transplant. 2016 Aug; 35(8):1024-30. doi: 10.1016/j.healun.2016.05.00. Epub 2016 May 6. Retrieved at: https://www.ncbi.nlm.nih.gov/pubmed/27316382

- Following continuous flow LVAD implantation, 23% of patients became allosensitized (defined as cPRA >10% in patients with pre-implantation cPRA of ≤10%). There was a higher risk of ACR and AMR among those who were bridged to heart transplantation with continuous flow LVAD compared to those who were not.

Kidambi S, et al. (2015) Clinical outcomes in sensitized heart transplant patients bridged with ventricular assist devices. Clin Transplant. 2015 Jun;29(6):499-505. doi: 10.1111/ctr.12540. Epub 2015 Apr 30. Retrieved at: https://www.ncbi.nlm.nih.gov/pubmed/?term=Clinical+outcomes+in+sensitized+heart+transplant+patients+bridged+with+ventricular+assist+devices.

- Sensitization appears to have a negative effect on mortality. This mortality appears to be concentrated in patients with AMR, and the authors postulate that the development of AMR in a sensitized patient may be a predictor of mortality.

5.8 Pre-transplant Considerations

Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: A 10-year update. J Heart Lung Transplant. 2016 Jan;35(1):1-23. doi: 10.1016/j.healun.2015.10.023. Retrieved at: https://www.ncbi.nlm.nih.gov/pubmed/?term=The+2016+International+Society+for+Heart+Lung+Transplantation+listing+criteria+for+heart+transplantation%3A+A+10-year+update

- Review of heart transplant listing criteria

5.9 Post-transplant Considerations

Punnoose LR, et al. (2020). Pregnancy outcomes in heart transplant recipients. J Heart Lung Transplant [Epub ahead of print.] Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/32201090

- Livebirths occurred in 69% of 157 reported pregnancies in 91 patients, and there were no neonatal deaths.
- The most common complications during pregnancy were preeclampsia (23%) and infections (14%). Rejection occurred during pregnancy in 9% and within 3 months postpartum in 7% of patients. Miscarriages occurred at a rate of 26%; 49% of patients who miscarried had mycophenolic acid exposure.

Alvarez-Alvarez RJ, Barge-Caballero E, Chavez-Leal SA, et al. (2015) Venous thromboembolism in heart transplant recipients: incidence, recurrence and predisposing factors. J Heart Lung Transplant. 2015 Feb;34(2):167-74. doi:10.1016/j.healun.2014.09.039. Epub 2014 Oct 2. Retrieved at: https://www.ncbi.nlm.nih.gov/pubmed/?term=Venous+thromboembolism+in+heart+transplant+recipients%3A+incidence%2C+recurrence+and+predisposing+factors.

- VTE is a frequent complication after HT, mainly during the first post-operative year. In view of a high recurrence rate, long-term anti-coagulation should be considered in HT recipients who experience a first VTE episode.

Wang YJ, et al. (2016.) Malignancy After Heart Transplantation Under Everolimus Versus Mycophenolate Mofetil Immunosuppression. Transplant Proc, 48(3):969-73. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Malignancy+After+Heart+Transplantation+Under+Everolimus+Versus+Mycophenolate+Mofetil+Immunosuppression.

- EVR treatment after heart transplant is associated with a lower risk of malignancy than is MMF treatment. The 2-year survival rate after malignancy was similar between EVR and MMF groups.

Ciarka A, et al. (2016). Effect of Heart Rate and Use of Beta Blockers on Mortality After Heart Transplantation. Am J Cardiol, 18(12):1916-1921. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=Effect+of+Heart+Rate+and+Use+of+Beta+Blockers+on+Mortality+After+Heart+Transplantation.

- In a large single-center cohort of HT recipients, higher heart rate and nonuse of β blockers were independently associated with higher mortality.

Jahangirifard A,et al. (2017) The Effect of Desmopressin on the Amount of Bleeding and Transfusion Requirements in Patients undergoing Heart Transplant Surgery. Basic Clin Pharmacol Toxicol, 121(3):175-80. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28326680

- Desmopressin may reduce postoperative bleeding in patients undergoing heart transplant surgery. Further studies are required to confirm the potential effect of desmopressin on establishing hemostasis following heart transplantation.

Fahrleitner-Pammer A, et al. (2017). Teriparatide treatment in a heart transplant patient with a chronic kidney disease and a low-turnover bone disease: a case report. Osteoporos Int, 28(3):1149-1152. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27988794

- Low-turnover bone disease is a complication of chronic kidney disease and a long-term steroid therapy. Currently, the only bone anabolic treatment available is teriparatide (TPTD). So far, no data exist in heart transplant patients, and only one single case with histomorphometric analysis of a dialysis patient with a low-turnover bone disease has been published. The current report shows the effect of a 1-year TPTD therapy in a cardiac transplant patient with 10 vertebral and 3 peripheral fractures who had developed a chronic kidney failure while receiving triple immunosuppressive therapy. A transiliac bone biopsy following tetracycline labeling was performed prior and after 1 year of treatment, showing an increase in the bone formation and improvement of the structural indices (20-fold increase of osteoid volume/bone volume, fourfold increase of osteoid surface/bone surface and increases of wall thickness (+15%), trabecular thickness (+9%), and trabecular number (+38%)). Bone mineral density was stable, no new vertebral fractures had occurred, the therapy was well-tolerated, and the patient improved clinically.

Bennett AL, (2017). Hypertension in Patients with Cardiac Transplantation. Med Clin North Am, 101(1):53-64. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27884235

- Hypertension affects more than 95% of patients. Increased blood pressure poses a significant cardiovascular morbidity and mortality in these patients; it should be identified quickly and needs to be managed appropriately. Understanding the pathophysiology and contributing factors to this disease in these complex and unique patients is the key to appropriate treatment selection

5.10 Miscellaneous Review Articles

Andrew J, Macdonald P. (2015) Latest developments in heart transplantation: a review. Clin Ther. 2015 Oct 1;37(10):2234-41. doi: 10.1016/j.clinthera.2015.08.019. Retrieved at: https://www.ncbi.nlm.nih.gov/pubmed/26497799

- A review of recently published literature in heart transplant.