5. Heart Transplantation

Table of Contents:

5.1 Induction therapy

Holzhauser L, et al. (2024). A heart transplant center experience with basiliximab induction strategies: A double edged sword? *Clin Transplant*. 2024 Apr;38(4):e15307. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38567897/

- Retrospective, single-center analysis of 475 heart transplant recipients to define the risks and benefits of induction with basiliximab. When adjusted for confounders, the basiliximab group was less likely to experience acute cellular rejection (ACR) (OR .42, $p<0.001$) but experienced increased incidence of antibody mediated rejection (AMR) (OR 11.7, $p<0.001$) and more CAV (OR 3.8, $p=.04$) than the no induction group. There was no difference in rates of infection or malignancy, but increased incidence of mortality found in the basiliximab groups. Basiliximab may reduce incidence of ACR but increases risk of AMR, CAV, and may be associated with increased risk of mortality.

Foroutan F, et al. (2024). Use of induction therapy post-heart transplantation: Clinical practice recommendations based on systematic review and network meta-analysis of evidence. *Clin Transplant*. 2024 Mar;38(3):e15270. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38445536/

- Clinical practice guideline on the use of induction therapy in heart transplant recipients produced from systematic review of current literature recommending no induction over basiliximab or rATG induction. If induction desired, then rATG is preferred to basixilimab.

Gupta SK, et al. (2023). Induction immunosuppression and post-transplant diabetes mellitus: a propensity-matched cohort study. *Front Endocrinol (Lausanne)*. 2023 Oct 20;14:1248940. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37929038/

- Keywords: IL2RA, basixilimab, thymoglobulin, rATG, alemtuzumab, diabetes
- Propensity matched cohort study of 7,421 US adults who received cardiac transplants between Jan 2009 and Dec 2018 using data from the SRTR database to evaluate the association between induction immunosuppression and post-transplant diabetes mellitus (PTDM). There was no association between induction immunosuppression and PTDM (HR 1.04, 95% CI 0.91-1.19). There were also no associations observed with each class of induction agents and PTDM. Use of induction immunosuppression was not shown to correlate with development of PTDM

Rudzik KN, et al. (2023). Basiliximab induction versus no induction in adult heart transplantation. *Clin Transplant*. 2023 May;37(5):e14937. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36793206/

- Retrospective, single-center cohort study to compare rejection, infection, and mortality within first year following heart transplant in patients receiving basiliximab versus no induction
- Retrospective, single-center cohort study of 134 adult heart transplant recipients between Jan 2017 and May 2021 to compare rejection, infection, and mortality within first year following heart transplant in patients receiving basiliximab versus no induction. Lower incidence of ACR within the first year in the basiliximab group versus no induction group (27.7 vs 68.2%, P<0.022). Basiliximab was associated with lower probability of rejection within first 12 months post-transplant (HR 0.285, 95% CI .142-.571, p<0.001). There was no difference in infection rates or mortality after discharge (6% vs 0%, p=0.20) at one-year post-transplant. Basiliximab was associated with greater freedom from rejection without an increase in infections.

Jennings, D, et al (2023). Impact of the United Network for Organ Sharing policy change on induction immunosuppression practice patterns and outcomes in adult heart transplant recipients. *Pharmacotherapy*. 43(2):115-121. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36588475/

- Retrospective analysis of how the new heart transplant allocation system has altered induction patterns and outcomes of heart transplant recipients. A total of 2775 patients were transplanted and received induction after the allocation change and 5070 were transplanted and received induction prior to the change. Basiliximab was the most commonly used induction agent (56%) though thymoglobulin was used more frequently after the allocation change than before (43.1% vs 37.2%, respectively). After the change in allocation system, 30-day mortality, 1-year mortality, and 1- year graft failure were all similar to before the change, though odds of a drug-treated rejection in the first year was lower under the new system.

Lee, G, et al (2022). . Retrospective Evaluation of Rabbit Antithymocyte Globulin Induction in Heart Transplant Patients. *Transplant Direct.* 8(6):e1329. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35651585/

- Retrospective study of adult transplant recipients given antithymocyte globulin for induction at a cumulative dose of 4.5 mg/kg (n=140) or <4.5 mg/kg (n=61). The primary outcome was the incidence of Grade 2 ACR or higher at 2 years. Adjusted all-cause mortality and ACR at 2 years for partial vs full induction was 3.31 [0.74-14.8] and 1.45 [0.62-3.37] respectively. There was no difference in rate of infections. Of note, those that got full induction were an average of 5 years younger.

Bellumkonda L, et al. (2022). The impact of induction therapy on mortality and treated rejection in cardiac transplantation: A retrospective study. J Heart Lung Transplant, S1053-2498(22)00006-7. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35094919/

- Retrospective analysis using UNOS database to compare outcomes of induction therapy with T cell depleting agents and IL2 receptor antagonists to no induction therapy. Compared to no induction therapy, induction with T cell depleting agent was associated with reduction in risk of treated rejection at 1 year with no effect on mortality. IL2 receptor antagonist was associated with a modest increase in mortality with no impact on risk of rejection.

Bubik RJ, et al. (2021) Malignancy among adult heart transplant recipients following patient-tailored dosing of anti-thymocyte globulin: a retrospective, nested case-control study of individualized dosing. Transpl Int, 34(11):2175-2183. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34411345/

- Single center, retrospective, matched, nested case-control study to determine the relative risk of rATG exposure with the actual incidence of malignancy post heart transplant.
- 25 out of 126 included patients experienced at least one post-transplant malignancy with an incidence rate of 23.8% at 5 years post-transplant. 14 patients had more than one malignancy. Median rATG cumulative dose in milligrams (mg) was 365 mg in cases and 480 mg in controls (per 100 mg: OR 0.90, 95% CI 0.75–1.08, *P* = 0.28); equivalent of median cumulative rATG dose of 4.7 mg/kg in cases vs. 5.8 mg/kg in controls (per 1 mg/kg: OR 0.92, 95% CI 0.78–1.09, *P* = 0.34). This study did not find a statistically significant correlation between malignancy and cumulative rATG exposure

Kitto B, et al. (2021). Rabbit Antithymocyte Globulin Induction in Heart Transplant Recipients at High Risk for Rejection. Ochsner Journal, 21(2), 133–138. Retrieved from: https://doi.org/10.31486/toj.20.0024

- Single-center retrospective cohort study comparing outcomes between high risk adult patients receiving rATG induction vs no induction from 2011-2017. 50 patients were included in the analysis and at one year the composite primary outcome of ≥2R rejection, any treated rejection, development of CAV, or graft loss was no different between groups. Infection rate was similar between group, but the rATG group had less prednisone exposure. This study concluded that rATG does not seem to improve allograft outcomes but can reduce early CCS exposure in patients at high immunologic risk.

Diaz-Castrillon CE, et al. (2021). Induction Immunosuppression and Renal Outcomes in Adult Heart Transplantation. Journal of Surgical Research, 259:14–23. Retrieved from: https://doi.org/10.1016/j.jss.2020.11.021

- Retrospective analysis using the UNOS database from 2000 to 2018 that evaluated the initiation of de novo dialysis after heart transplantation and the relationship between induction immunosuppression and pre transplant eGFR with post-transplant outcomes. Adjusted multivariable analysis found that induction therapy was associated with de novo dialysis with the most significant effect on patients with eGFR ≥ 60. Overall, the use of induction immunosuppression in orthotopic heart transplantation did not correlate strongly with pre-transplant eGFR and did not mitigate the risk of RRT post-transplant.

Skoric B, et al. (2021). Lower Platelet Count Following Rabbit Antithymocyte Globulin Induction Is Associated With Less Acute Cellular Rejection in Heart Transplant Recipients. Transplantation Proceedings, 53(1):335–340. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32571710/

- This was a retrospective single center cohort study that included 156 heart transplant patients who received rATG induction. They found that during the 24 month follow-up period, patients with ACR had significantly higher platelet counts on day 7 and higher ALC on day 14. They concluded that lower platelet count after induction with rATG is associated with less ACR

Watanabe T, et al. (2020). Influence of Induction Therapy Using Basiliximab With Delayed Tacrolimus Administration in Heart Transplant Recipients — Comparison With Standard Tacrolimus-Based Triple Immunosuppression. Circulation Journal, 84(12), 2212–2223. Retrieved from: https://doi.org/10.1253/circj.cj-20-0164

- This retrospective study looked at the influence of induction therapy using basiliximab with delayed FK initiation on outcomes in high-risk heart transplant recipients. Included 86 recipients, 46 of those were included in the induction group (impaired renal function, pre-transplant sensitization, recipient/donor risk factors) and FK administration was delayed. Induction group patients had lower incidence of ACR, but this was not statistically different. Renal function was significantly improved in the induction group, and this group had a significantly increased risk of bacterial or fungal infections. Therefore, basiliximab induction with delayed FK initiation may suppress ACR and improve renal function in high-risk heart transplant recipients.

Nozohoor S, et al. (2020). Induction immunosuppression strategies and long-term outcomes after heart transplantation. Clinical Transplantation, 34(7):e13871. Retrieved from: https://doi.org/10.1111/ctr.13871

- This study analyzed data from the ISHLF registry for adult heart transplants performed between 2000 and 2013 to look at cumulative all-cause mortality of patients who received no induction, induction with basiliximab, or induction with ATG. Included over 27,000 recipients and found survival was similar in patients treated with no induction compared with ATG, but survival was improved using no induction over basiliximab. Basiliximab was associated with higher risk of graft failure related deaths, and ATG was associated with higher risk of malignancy related deaths.

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.

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.

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.

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

Pearston AP, et al. (2023). Conversion to tacrolimus alone compared to full immunosuppression following cardiac transplantation (TACTFUL). *Clin Transplant*. 2023 Dec;37(12):e15140. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37733704/

- Single-center, retrospective cohort study of 112 adult heart transplant recipients from Jan 2015 to July 2021 to compare outcomes among patients transitioned to tacrolimus monotherapy vs combination therapy (tacrolimus, mycophenolate, and prednisone)
- Most common reasons for conversion to monotherapy were leukopenia, infection, and GI distress. No statistically significant difference in mortality (0 in monotherapy vs 11 in combination therapy, p=0.09) or percentage of patients with 2R/3R rejection (24% in monotherapy vs 32.2% in combination therapy, p=0.43). No monotherapy groups experienced rejection after converting from combination therapy. 24% of patients in the monotherapy group resumed at least another additional immunosuppressant.

Baran DA, et al. (2023). Long term follow-up of the tacrolimus in combination, tacrolimus alone compared (TICTAC) trial. *J Heart Lung Transplant*. 2023 Jun;42(6):838-845. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36870863/.

- Long-term results from a prospective, randomized trial of 147 initial heart transplant recipeints from the TICTAC trial comparing tacrolimus monotherapy to tacrolimus plus mycophenolate mofetil
- Post-transplant survival at 5, 10, and 15 years in the TAC monotherapy was 84.5%, 66.9%, and 52.7% compared to 94.4%, 78.2%, and 56.1% in the TAC/MMF combination group (p=0.19). Freedom from CAV was 100%, 87.5%, 69.3%, and 46.5% at 1, 5, 10 and 15 years in the tacrolimus monotherapy group compared to 100%, 76.9%, 68.1%, and 54.4% in the TAC/MMF group (p=0.96). Freedom from dialysis or renal replacement was 92.8%, 84.2%, and 68.4% for TAC monotherapy versus 100%, 93.4%, and 82.3% for the TAC/MMF patients as 5, 10, and 15 years post-transplant. The best outcomes were noted for patients initiated on TAC/MMR including patients who had MMF discontinued for intolerance.

Nanni AN, et al. (2021). Association of tacrolimus time-to-therapeutic range on renal dysfunction and acute cellular rejection after orthotopic heart transplantation in a high use basiliximab population. Clin Transplant, e14542. Retrieved from: https://doi.org/10.1111/ctr.14542

- Single-center retrospective cohort study in the US from July 2013 to April 2020.
- 46.6% of patients in the study population developed new renal dysfunction after tacrolimus was initiated. Patients who developed new renal dysfunction had a shorter time from transplant to time-to-tacrolimus (TTT) than those who did not develop renal dysfunction (11.6 vs. 13.0 days, p = 0.07). However, supratherapeutic tacrolimus levels occurred more frequently in the patients who developed new renal dysfunction (56% vs. 39.2%, p = 0.01).
- Acute cellular rejection (ACR) occurred in 36.9% of patients within 30 days after OHT. There was no significant difference in TTT between the patients who developed ACR and those who did not (11.1 vs. 10.8 days, p = 0.638).

Shiraishi Y, et al. (2020). Impact of tacrolimus versus cyclosporin A on renal function during the first year after heart transplant. ESC Heart Failure, 7(4), 1842–1849. Retrieved from: https://doi.org/10.1002/ehf2.12749

- This was a retrospective study looking at 72 patients receiving de novo heart transplants at a single center to assess FK vs CsA with clinical outcomes with a focus on nephrotoxicity. In the first year post transplant, 59% of patients in the FK group switched mycophenolate to everolimus, and only 48% in the CsA group switched. There were no differences in renal function or graft rejection within 1 year post transplant between the FK and CsA groups. This study concluded that irrespective of everolimus use with low-dose CNIs, there were no differences in renal function as well as graft rejection during the first year after HTx between HTx recipients who received TAC or CsA.

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.

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

Alam A, et al. (2021). Impact of risk-stratified mycophenolate dosing in heart transplantation. Clinical Transplantation. Published. Retrieved from: https://doi.org/10.1111/ctr.14445

- This was a retrospective single-center study that analyzed 140 consecutive heart transplant patients who were initiated on a risk-stratified MMF protocol post-transplant. The study concluded that the composite rate of BPAR, graft loss, or mortality at 1-year post-transplantation was similar between the two groups. Incidence of neutropenia, thrombocytopenia, infection, cardiac allograft vasculopathy, or acute kidney injury by 1-year also showed similar results between the two groups. This study concluded that risk-stratification of MMF dosing appears to be a safe and effective strategy after heart transplantation.

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

Kancharla M, et al. (2024). Drug levels after sirolimus initiation and short-term outcomes in ambulatory heart transplantation recipients. *Clin Transplant*. 2024 Jan;38(1):e15184. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37933602/

- Retrospective analysis of 99 adult heart transplant recipients to assess impact of relative change in combined drug levels of sirolimus and tacrolimus on GFR, LVEF, DSA, ACR, and all-cause mortality.
- 9 patients had decreased, 15 stable, and 75 increased relatively combined drug levels. Change in eGFR was higher in patients with decreased levels compared to increased combined levels ($p<.05$) but was not sustained at 12 months. There were no differences in LVEF change or individual/composite risks for developing DSa, ACR, and all-cause mortality at 12 months.

Almond CS, et al. (2023). The teammate trial: Study design and rationale tacrolimus and everolimus against tacrolimus and MMF in pediatric heart transplantation using the major adverse transplant event (MATE) score. *Am Heart J*. 2023 Jun;260:100-112. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36828201/

- First multicenter randomized clinical trial in pediatric heart transplant to evaluate the safety and efficacy of everolimus and low-dose tacrolimus compared to standard-dose tacrolimus and mycophenolate mofetil. Study publication pending.

Sperry BW, et al. (2023). Stabilization of Rapidly Progressive Cardiac Allograft Vasculopathy Using mTOR Inhibition After Heart Transplantation. J Card Fail. 2024 Apr;30(4):613-617. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37992800/

- Retrospective study of 216 adult heart transplant recipients to investigate associations between mTORi initiation and progression of CAV
- 81 (37.5%) patients were switched from MMF to SRL after 1 year with 34 (42%) due to rapidly progressive CAV. mTOR inhibition was associated with reduction in intimal thickness by 0.05 mm (95% CI 0.02-0.07, $p<0.001$), but was no associated with a decrease in long-term cardiovascular adverse events ($p=0.669$).

Asleh R, et al. (2022). Sirolimus-Based Immunosuppression Is Associated with Decreased Incidence of Post-Transplant Lymphoproliferative Disorder after Heart Transplantation: A Double-Center Study. J Clin Med, 11(2):322. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35054016/

- A retrospective review comparing risk of PTLD in sirolimus-based to calcineurin-inhibitor based immunosuppressive regimens. EBV mismatch was strongly associated with increased risk of PTLD ($p<0.001$), and conversion to sirolimus was protective against development of PTLD ($p=0.02$) even after adjusting for EBV mismatch ($p=0.006$).

Asleh R, et al. (2021). Effects of mTOR inhibitor-related proteinuria on progression of cardiac allograft vasculopathy and outcomes among heart transplant recipients. Am J Transplant, 21(2):626-635. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32558174/

- Single Single center, non-randomized, retrospective cohort performed in the United States from 1994 to 2016. The aim of this study was to determine if conversion to sirolimus-related proteinuria led to progression of cardiac allograft vasculopathy (CAV).The proteinuria group had significantly more severe CAV (grade 0 27.8%, grade 1 61.1%, grade 2 8.3%, grade 3 2.8%) compared to the non-proteinuria group (grade 0 47.5%, grade 1 50.5%, grade 2 1.0% grade 3 1.0%) ($p = 0.037$).

- Proteinuria after starting sirolimus was associated with increased all-cause mortality compared to the non-proteinuria group for both unadjusted and adjusted analyses (p = 0.021 and p = 0.01, respectively).

Eisen HJ. (2021). CAVEAT mTOR: You've heard about the benefits of using mTOR inhibitors, here are some of the risks. Am J Transplant, 21(2):449-450. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32715588/

- Review article discussing the adverse effects of mTOR inhibitors in patients who have received a cardiac transplant.

Sallam K, et al. (2021). Sirolimus Adverse Event Profile in a Non-Clinical Trial Cohort of Heart Transplantation Patients. Annals of Transplantation, 26:e923536. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33462174/

- Retrospective study assessing the differences in ADEs in 221 adult HTRs who received either sirolimus or MMF. There was a statistically significant difference in rates of ADEs with 71% of patients in the sirolimus arm as compared to 40% in the MMF arm ($p<0.01$). Sirolimus had a higher incidence of elevated triglycerides, LLE, and oral ulcerations and was discontinued in 22% of patients.

Anthony C, et al. (2021). Everolimus for the Prevention of Calcineurin-Inhibitor-Induced Left Ventricular Hypertrophy After Heart Transplantation (RADTAC Study). JACC: Heart Failure, 9(4), 301–313. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33795116/

- Prospective, randomized, open-label study in which OHT recipients were randomized at 12 weeks post transplant to low-dose everolimus and FK (RADTAC) or standard dose FK group (TAC) (both groups received MMF and prednisone). There was a significant decrease in left ventricular mass in the RADTAC group compared to TAC group (-13.0 $\pm$ 16.8 g v. 2.1 $\pm$ 8.4 g, $p<0.001$).There were also significant differences in function and fibrosis which were higher in the low dose everolimus group. There were no differences in blood pressure, renal function, rejection, or infections.

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

- Retrospective, single-center study comparing post-HT maintenance strategies of TAC, MMF and steroids v. a CNI-free everolimus regimen. There were non-significant differences in survival rate, rejection rate, and infections between groups 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.

- Study examining a subgroup of patients from the SCHEDULE trial to assess the development of albuminuria in de novo-treated EVR v. CNI patients and the association with renal function. 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

- Retrospective study investigating effects of sirolimus therapy on PCSK9 levels in HTRs. A switch from CNI to sirolimus 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 ($p = 0.2$).

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

- Open-labeled, multicenter RCT comparing outcomes of everolimus with CNI withdrawal v. CNI-based immunosuppression in HTRs. There was no significant change in measured glomerular filtration rate (mGFR) from baseline to year 3 post randomization between groups. No difference was found between all-cause mortality, major cardiovascular events, or treated acute rejection between the two groups. 34.5% of HTRs in everolimus group discontinued study drug due to ADEs.

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.

- Randomized, open-label trial, de novo HTRs examining 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. (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.

5.2.5 Belatacept

Oren D, et al. (2024). Utility of a fusion protein T-cell co-stimulation blocker Belatacept in heart transplant recipients: Real world experience from a high volume center. *Clin Transplant*. 2024 Mar;38(3):e15251. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38504576/

- Retrospective cohort study of 21 heart transplant recipients to retrospectively analyze the use of belatacept (BTC) in two distinct patient populations BTC dosing was 5mg/kg every 2 weeks for 3-5 doses followed by 5mg/kg monthly and used in conjunction with reduced dose CNI.Primary indications for BTC use were elevated pre-formed DSA in highly sensitized patients (67%) and renal sparing (24%), One patient encountered 2R rejection within 1 year of starting BTC. Graft function remained stable at 6 and 12 months following treatment. Infections occurred in 52.4% of patients with 19% requiring discontinuation of therapy.

Bilgili E, et al. (2023). Belatacept as Primary Maintenance Immunosuppression in Heart Transplant recipients: A Single Center Experience. Journal of Heart and Lung Transplantation, 42(4):S426-4227. Retrieved from: https://www.sciencedirect.com/science/article/pii/S1053249823011440

- Abstract only. Eleven patients received belatacept for CNI sparing due to renal (55%) or neurotoxic (45%) adverse effects. Seven patients (64%) experienced any rejection and six (55%) experienced at least one AMR episode.

Uriel M, et al. (2022). The Efficacy and Safety of Belatacept in Heart Transplant Recipients. Journal of Heart and Lung Transplantation, 41(4):S338. Retrieved from: https://www.jhltonline.org/article/S1053-2498(22)01418-8/fulltext

- Abstract only. Retrospective analysis of patients who underwent heart transplant and received belatacept (n=21). Belatacept was initiated at a median of 22.6 months after heart transplant. Only 1 patient experienced grade 2R rejection in the 12 months following belatacept initiation. A total of 33.3% experienced infection and 4 patients were changed back to a CNI. Serum creatinine improved from a median of 1.58 [1.0-2.1] to 1.45 [1.1-1.9].

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

Oreschak K, et al. (2021). Variants in mycophenolate and CMV antiviral drug pharmacokinetic and pharmacodynamic genes and leukopenia in heart transplant recipients. The Journal of Heart and Lung Transplantation, 40(9), 917–925. Retrieved from: https://doi.org/10.1016/j.healun.2021.05.020

- This was a retrospective analysis of 148 heart transplant patients who received mycophenolate and an antiviral against CMV to determine the relationship between SNPs in mycophenolate and CMV antiviral drug PK/PD genes and drug-induced leukopenia. Drug induced leukopenia occurred in ~20% of patients with the a specific HNF1A rs1169288 polymorphism association in the first 6 months post-transplant. Variant C allele carriers had significantly higher odds of leukopenia than A/A homozygotes. This study concluded that genetic variation may play a role in the development of leukopenia in patients receiving mycophenolate or antivirals for CMV following heart transplantation and this genetic marker could help identify patients at risk.

5.3 Desensitization therapy

Jung R, et al. (2024). Improved Graft Function following Desensitization of Anti-AT1R and Autoantibodies in a Heart Transplant Recipient Negative for Donor-Specific Antibodies with Antibody-Mediated Rejection: A Case Report. Int J Mol Sci. 2024 Feb 12;25(4):2218. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38396895/

- Case report of a heart transplant recipient with anti-AT1R antibody-induced AMR suggesting the need for pre-transplant testing of non-HLA antibodies

Fida N, et al. (2024). Effectiveness of combined plasma cell therapy and costimulation blockade based desensitization regimen in heart transplant candidates. Clin Transplant. 2024 Feb;38(2):e15249. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38369810/

- Case report of 5 patients with cPRA ≥50% (with ≥3 antibodies of ≥5000 MFI) who underwent desensitization with plasma cell depletion (proteasome inhibitor or daratumumab) and costimulation blockade (belatacept).

Dhillon M, et al. (2024). Does bortezomib influence pre-transplant desensitization therapy or benefit post-heart transplant outcomes for highly sensitized patients. Clin Transplant, e15165 [Online ahead of print]. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37837612/

- Non-randomized, open-label trial including 43 highly sensitized patients age≥ 18 years between 2010 and 2021 with cPRA >50% who received plasma exchange and four rounds of bortezomib prior to transplantation. There was no significantly lower circulating antibodies prior to heart transplantation. Compared to a control group of non-sensitized patients patients treated with bortezomib had similar 1 year survival (95.4% v. 92.5%) but with increased incidence of AMR (79.1% v. 97.1%, p <0.001), any treated rejection (62.8.% v. 86.7%, p<0.001) and de novo DSA development (81.4% v. 92.5%, p=0.007).

Baez Hernandez N, et al. (2023). New Desensitization Strategy: Daratumumab for Highly Sensitized Pediatric Heart Transplant Candidate. Transplantation, 107(10):e271-272. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37749815/

- Case report detailing successful use of daratumumab in 13-mo-old girl with a persistent cPRA 99% allowing for subsequent transplantation.

Brinkley DM, et al. (2023). Efficacy of bortezomib desensitization among heart transplant candidates. Clin Transplant, 37(4):e14907. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36661196/

- Retrospective study reviewing HTRs with cPRA>50% who underwent a bortezomib desensitization therapy from 2016 to 2021. The protocol included plasma exchange for 3 days, followed by IVIG 2g/kg and up to 4 rounds of bortezomib. There was a significant decrease in HLA class 1 antibodies (21-15, p=0.001) but not class II antibodies. One year survival following transplant was 89% with a 33% rate of antibody-mediated rejection.

Youn JC, et al. (2023). Three-year post heart transplant outcomes of desensitized durable mechanical circulatory support patients. J Heart Lung Transplant, 41(10): 1408-1414. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37150473/

- Single-center prospective, observational analysis comparing patients who underwent HT between 2010 and were either (A) desensitized mechanical circulatory support patients, (B) desensitized non-mechanical support patients, or (C) any non-desensitized patents. Desensitization included combinations of rituximab/IVIG and plasmapheresis/bortezomib. Group A showed a higher PRA reduction after desensitization than group B (-22.2 + 26.9 v. -6.3 +7.5, p=0.015). Groups A and C showed comparable primary graft dysfunction, 3-year survival, freedom from cardiac allograft vasculopathy, etc.

Kittleson MM. Management of the sensitized heart transplant candidate. Curr Opin Organ Transplant. 2023 Oct 1;28(5):362-369. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37678171/

- Review article discussing modern advances in desensitization of heart transplant recipients

Brinkley DM, et al. (2023). Efficacy of bortezomib desensitization among heart transplant candidates. Clin Transplant. 2023 Apr;37(4):e14907. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38396895/

- Analysis describing the efficacy of bortezomib desensitization and subsequent impact on post-transplant outcomes
- n= 25 patients listed for heart transplant with cPRA >50% between 2016 and 2021 receiving desensitization with plasma exchange, intravenous immunoglobulin, and bortezomib
- After desensitization, all C1q antibodies were removed from a candidate's unacceptable antigen list. There was a significant decrease in the median number of HLA class I (p=.001) but not HLA class II antibodies (p=.07). There was a significant decrease in the median cPRA antibodies for class I (p=.004) but not class II (p=.30). After desensitization, 76% of patients were transplanted. One-year survival was 89% with a 33% rate of AMR. Bortezomib was modestly effective for class I antibodies and allowed successful transplant in most patients.

Sommer W, Avsar M, Aburahma K, et al. Heart transplantation across preformed donor-specific antibody barriers using a perioperative desensitization protocol. Am J Transplant. 2022;22:2064–2076. doi:10.1111/ ajt.17060.

Habal, MV (2021). Current Desensitization Strategies in Heart Transplantation. Frontiers in Immunology, 12:702186. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34504489/

- This review article discusses tailoring approaches to desensitization in heart transplant recipients through further attention to B cell activation, memory, and plasma cell differentiation to establish methods that durably abrogate the anti-HLA antibody response before and after transplant.

Sriwattanakomen R, et al. (2021). Impact of carfilzomib-based desensitization on heart transplantation of sensitized candidates. The Journal of Heart and Lung Transplantation, 40(7):595–603. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33785250/

- This was a study using carfilzomib for desensitization in heart transplant recipients. They included 9 patients that underwent 20 cycles of carfilzomib based desensitization and found an average cPRA decrease of 24% for IgG and 36% for C1q. Overall from treatment start to finish, mean cPRA fell from 76% to 40% for IgG (p=0.01) and 56% to 4% for C1q (p=0.017). All patients survived within the follow up time of 35.1 months with only 1 instance of rejection. AKI and thrombocytopenia were the most common side effects both self-resolving.

Saadi TA, et al. (2021). Outcomes of pre- heart transplantation desensitization in a series of highly sensitized patients bridged with left ventricular assist devices. The Journal of Heart and Lung Transplantation, 40(10):1107–1111. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34281777/

- This retrospective study assessed LVAD bridged candidates who received pre-transplant desensitization therapy with IVIG and rituximab followed by bortezomib and PLEX if insufficient

response. Of the 10 patients analyzed, median decreased in cPRA was 11% with no significant decrease for 3 patients. All patients had ADEs including coagulopathy, bone marrow suppression, and infection. One patient had rejection and 3 had rising DSAs.

Nguyen LS et al. (2021). Impact of Sex in the Efficacy of Perioperative Desensitization Procedures in Heart Transplantation: A Retrospective Cohort Study. Frontiers in Immunology, 12:659303. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34305891/

- Retrospective cohort study that assessed the effect of desensitization by comparing treated patients to a historical control. The study included 68 patients and found significant protective association between desensitization and events and a deleterious association between cumulative preformed donor-specific DSA and events. There was also a sex difference in the efficacy of desensitization where in men the benefit was significant but not in women. In conclusion, perioperative desensitization was associated with fewer AMR/deaths after transplant with efficacy more pronounced in men.

Plazak ME, et al. (2021). Clinical Outcomes of Perioperative Desensitization in Heart Transplant Recipients. Transplantation Direct, 7(2), e658. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33521247/

- Single center, retrospective study of adults who received heart transplant and perioperative desensitization if virtual crossmatch or flow-cytometry crossmatch was positive. Patients received PLEX, IVIG, and rATG compared with historical controls with standard immunosuppression or induction. Of the 104 patients included, 10 received desensitization and there were no differences in the primary endpoint of survival at 12 months. Rates of acute rejection were lower with induction and desensitization than no induction. There were no differences in CAV.

Alishetti S, et al. (2020). Desensitizing highly sensitized heart transplant candidates with the combination of belatacept and proteasome inhibition. American Journal of Transplantation, 20(12), 3620–3630. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32506824/

- This study treated 4 highly sensitized heart transplant candidates with belatacept and PI therapy and found a significant reduction in both class I and II HLA antibodies and an increased likelihood of identifying an acceptable donor. This study found synergism between PI based desensitization and belatacept facilitating transplantation with a negative CDC crossmatch against C1q binding antibodies.

Timofeeva OA, et al. (2020). Serum dilutions as a predictive biomarker for peri-operative desensitization: An exploratory approach to transplanting sensitized heart candidates. Transplant Immunology, 60: 101274. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32142756/

- This study investigated sera dilutions as a potential to guide therapeutic plasma exchange regimens for effective peri-operative desensitization and early AMR treatment in heart transplant patients. The data revealed that 1:16 dilutions of EDTA-treated sera and 1.5 volume TPE reduced anti-HLA class I/class II antibody levels and allowed the investigators to predict which antibodies would respond to peri-operative plasma exchange. Using their results, they transplanted three highly sensitized cardiac recipients with peri-operative desensitization based on a virtual crossmatch performed on 1:16 diluted serum, and have used sera dilutions to guide DSA treatment post-transplant.

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.

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

Afzal A, et al. (2022). Observed elevated donor-derived cell free DNA in orthotopic heart transplant recipients without clinical evidence of rejection. Clin Transplant, 36(3):314549. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34863042/

- Retrospective cohort study evaluated possible confounders warranting the need for more intelligent use of this non-invasive surveillance technique. Recipients who experienced dd-cfDNA ≥ 0.20% in the absence of clinical rejection were analyzed and revealed four distinct groups characterized by (a) subclinical rejection with 50% CMV (n = 16), (b) non-CMV infections and the longest time to first elevated dd-cfDNA (187 days) (n = 8), (c) right ventricular dysfunction (n = 6), and (d) women who showed the youngest median age (45 years) and highest median dd-cfDNA (0.50%) (n = 5).

Kewcharoen J, et al. (2022). Initiation of noninvasive surveillance for allograft rejection in heart transplant patients > 1 year after transplant. Clin Transplant, 36(3):e14548. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34843112/

- This retrospective cohort study described their use of gene expression profiling (GEP) and dd-cfDNA in heart transplant recipients > 1-year post-transplantation. Among nine EMBs, one sample showed acute cellular rejection grade 2R due to elevations of both GEP and dd-cfDNA. This study showed use of both GEP and dd-cfDNA led to an increased number of EMB in patients > 1-year post-transplantation.

Knuttgen F, et al. (2022). Graft-derived cell-free DNA as a noninvasive biomarker of cardiac allograft rejection: a cohort study on clinical validity and confounding factors. Transplantation, 106(3):615-622. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33653997/

- Prospective cohort study included 87 patients and 770 serial dd-cfDNA samples drawn at predefined time-points. The study found dd-cfDNA plasma values were significantly associated with cardiac rejection. Confounding factors identified included pericardial effusions and improper sampling (e.g. shortly after biopsy) which should be considered when dd-cfDNA is used for rejection diagnoses.

Qian X, et al. (2022). Noninvasive biomarkers in heart transplant: 2020–2021 year in review. Current Opinion in Organ Transplantation. 2022;27(1):7-14. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34939959/

- This article reviewed recent advances in the field of noninvasive biomarkers to detect allograft rejection after heart transplant. Noninvasive biomarkers discussed include donor-derived cell-free DNA (dd-cfDNA), MicroRNAs, high-sensitive cardiac troponin (hs-cTnI), N-terminal pro-brain natriuretic peptide (NTproBNP), donor-specific antibodies (DSAs), and circulating extracellular vesicles (EVs)

Slomovich S, et al. (2021). Extracorporeal photopheresis and its role in heart transplant rejection: prophylaxis and treatment. Clinical Transplantation, 35(7):e14333. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33914369/

- This review discusses extracorporeal photopheresis and summarizes the current data on its use for prophylaxis and therapy in heart transplant rejection.

Boutolleau D, et al. (2021). Association between cytomegalovirus infection and allograft rejection in a large contemporary cohort of heart transplant recipients. Transplant Infectious Disease, 23(4):e13569. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33452851/

- This was a single center cohort study that utilized a database of heart transplant patients to determine association between CMV and allograft rejection. Out of the 384 patients included, there was no association between CMV and rejection

Peyster EG, et al. (2020). In Situ Immune Profiling of Heart Transplant Biopsies Improves Diagnostic Accuracy and Rejection Risk Stratification. *JACC: Basic to Translational Science*, *5*(4):328–340. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32368693/

- This was a retrospective cohort of clinical endomyocardial tissue samples that found that in situ immune modulators (such as ligand 1+, 68+ cells, forkhead box P3+ regulate the severity of cardiac allograft rejection.

Itoda Y, et al. (2020). Ventricular assist device bridging with gender-mismatch increases rejection and decreases survival following a heart transplant. European Journal of Cardio-Thoracic Surgery, 59(1):217–225. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33057607/

- This study obtained data from the UNOS database and divided patients into VAD recipients who received a heart from a gender matched donor (VAD-M), VAD recipients who received a heart from a gender mismatched donor (VAD-MM), noVAD recipients who received a heart from a gender matched donor (noVAD-M), and noVAD recipients that received a heart from a gender mismatched donor (noVAD-MM). They found in an adjusted survival analysis that the VAD-MM

group showed significantly worse survival than the VAD-M group with no difference between the noVAD-M and noVAD-MM groups.

Adamson MB, et al. (2020). HLA-G +3196 polymorphism as a risk factor for cell mediated rejection following heart transplant. Human Immunology, 81(4):134–140. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31928922/

- HLA-G expression is associated with rejection and this study objective was to evaluate polymorphisms and cell mediated rejection (CMR). 123 recipients were randomized to identify polymorphisms, they found the CG genotype polymorphism was associated with reduced CMR risk and the +3196 G allele was a risk factor for CMR.

Osorio-Jaramillo E, et al. (2020). Molecular-level HLA mismatch is associated with rejection and worsened graft survival in heart transplant recipients – a retrospective study. Transplant International, 33(9):1078–1088. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32441827/

- This was a retrospective study to look at HLA mismatching with post-transplant graft survival, rejection, and CAV. They analyzed 1167 patients and found that patients with a higher HLA-DR AMM load had inferior 1 year graft survival. They also found that HLA-AB increasing load had a higher risk of rejection.

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

Halloran PF, et al. (2022). Many heart transplant biopsies currently diagnosed as no rejection have mild molecular antibody-mediated rejection-related changes. J Heart Lung Transplant, 41(3):334-344. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34548198/

- Study extended the Molecular Microscope (MMDx) methodology to define a new “Minor” category characterized by low-level inflammation in non-rejecting biopsies and found many heart transplants currently diagnosed as no-rejection by histologic or molecular assessment have minor increases in ABMR-related and IFNG-inducible transcripts, associated with DSA positivity and mild histologic inflammation.

Nelson LM, et al. (2020). Mild acute cellular rejection and development of cardiac allograft vasculopathy assessed by intravascular ultrasound and coronary angiography in heart transplant recipients—a SCHEDULE trial substudy. Transplant International, 33(5):517–528. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31958178/

- This study evaluated the associated between ACR and development of CAV after heart transplant. It is a substudy of SCHEDULE which included 115 patient who received everolimus w/ CNI elimination or CNI based immunosuppression. They found that ACR was recorded in 67% of patients and median maximal intimal thickness was not different between ACR and no ACR groups. The incidence of CAV was no difference between groups.

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

Pottebaum AA, et al. (2024). Feasibility of Interleukin-6 Receptor Blockade in Cardiac Antibody-mediated Rejection. Transplantation. 2024 Feb 1;108(2):539-544. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37638881/

- Case report describing initial use of interleukin-6 receptor blockade with tocilizumab in treatment of acute cardiac AMR

Marco I, et al. (2023). De Novo Donor-Specific Antibodies after Heart Transplantation: A Comprehensive Guide for Clinicians. J Clin Med. 2023 Dec 2;12(23):7474. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10707043/

- Review of existing data about de novo DSA with the aim of providing a helpful framework for clinicians to help decision making and future investigations.

Horn ET, et al. (2023). Reduction of HLA donor specific antibodies in heart transplant patients treated with proteasome inhibitors for antibody mediated rejection. Clin Transplant. 2023 Dec;37(12):e15132. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37705362/

- Retrospective review to summarize data using proteasome inhibitor-based regimen to treat AMR in heart transplant recipients

Saldan A, et al. (2023). Human cytomegalovirus and Epstein-Barr virus infections occurring early after transplantation are risk factors for antibody-mediated rejection in heart transplant recipients. Front Immunol. 2023 May 15;14:1171197. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37256129/

- Case-control study to investigate the potential role of early-onset active CMV and EBV infections as risk factors for AMR
- n=47 heart transplant recipients diagnosed with AMR in study group and 23 patients without serologic/bioptic or clinical evidence of AMR
- Observed a positive statistical association between CMV and EBV infections (p=0.0136) and between EBV infection and AMR (p=0.0034). Findings suggest the role of CMV and EBV as risk factors for AMR in heart transplant.

Giarraputo A, et al. (2023). Banff Human Organ Transplant Consensus Gene Panel for the Detection of Antibody Mediated Rejection in Heart Allograft Biopsies. Transpl Int. 2023 Sep 4;36:11710. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37745639/

- Study to analyze in silico ability of the Banff Human Organ Transplant Panel to capture relevant genes, pathways, and networks associated with AMR compared to the whole-transcriptome analysis.

Coutance G, et al. (2023). Intermediate-term outcomes of complement inhibition for prevention of antibody-mediated rejection in immunologically high-risk heart allograft recipients. J Heart Lung Transplant. 2023 Oct;42(10):1464-1468. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37182818/

- Prospective evaluation of a single-center, single-arm, open-label trial to assess the efficacy and safety of complement inhibition at transplant in highly sensitized heart transplant recipients.
- n=20 adult heart transplant recipients with PRA >70% and preformed DSA receiving eculizumab during first 2 months post-transplant
- After the first year or transplant, there were no episodes of pAMR2 or greater and no left ventricular dysfunction. There were 3 deaths, 1 episode of pAMR1, and 1 patient with minimal de

novo CAV. There was a non-statistically significant benefit of eculizumab with lower incidence of the primary end-point or death.

Kim PJ, et al. (2023) Antibody Mediated Rejection is not Associated with Worse Survival in Adherent Heart Transplant Patients in the Contemporary Era. medRxiv [Preprint]. 2023 Dec 8:2023.12.01.23299311. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38106112/

- Retrospective, single-center study to evaluate the clinical significance associated with C4d and/or DSA positivity in adult heart transplant patients with respect to clinical outcomes in the contemporary era (2010 to current).
- n=560 adult heart transplant patients with C4d and DSA testing performed
    - Exclusion criteria: patients diagnosed with AMR without positive C4d immunofluorescence
- There was no significant difference in all-cause mortality or cardiac retransplant between the four groups studied (p=0.11). The risk for cardiac mortality or retransplant was significantly higher in C4d+/DSA+ versus C4d-/DSA- patients (HR=4.73, p=0.042) but not significantly different in C4d+/DSA- versus C4d-/DSA- patients (p=1.00). Medically adherence C4d+/DSA+ heart transplant patients show significantly greater risk for allograft dysfunction but not mortality or retransplant.

Boulet J, et al. (2023). Outcomes of untreated subclinical antibody-mediated rejection after heart transplantation. Prog Cardiovasc Dis. 2023 Nov-Dec;81:48-53. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37827423/

- Retrospective, case control study to investigate whether subclinical AMR group would have similar long-term patient and allograft outcomes after a diagnosis of pathological AMR compared to control heart transplant recipients without evidence of AMR
- n=260 adult heart transplant recipients at Brigham and Women's Hospital between May 2004 and Feb 2021
- The mortality rate was higher in controls compared to the subclinical AMR group (HR 0.66; CI 0.18-2.36). The combined rate of CAV, graft dysfunction, or mortality was higher in the subclinical AMR group than in controls (HR 1.63, CI 0.07-40.09). This study suggests that subclinical AMR diagnosed in the first year after heart transplant on surveillance biopsy isn't associated with decreased survival.

Marek-Iannucci S, et al. (2023). COVID-19 associated development of antibody mediated rejection in orthotopic heart transplantation patients. Clin Transplant. 2023 Aug;37(8):e14906. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36610020/

- Case description of 3 patients who developed AMR after mild COVID-19 infection or vaccination in heart transplant recipients

Yopes M, et al. (2022).Chronic intermittent intravenous immunoglobulin in heart transplant recipients with elevated donor-specific antibody levels. Clinical Transplantation. 2022;36(2). Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34705286/

- Retrospective cohort study evaluated 19 patients receiving chronic intermittent IVIG for elevated DSA that examined changes in DSA, MFI and allograft function (LVEF, CI)

Yerly P, et al. (2022). Complement blockade with eculizumab to treat acute symptomatic humoral rejection after heart transplantation. Xenotransplantation, 29(1):e12726. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35001433/

- Case report of a heart transplant recipient presenting with late acute AMR. The patient fully recovered allograft function and completely cleared DSA following plasmapheresis-free upfront eculizumab administration along with thymoglobulin, IVIG, and rituximab.

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

Patel K, et al. (2024). High sensitivity troponin I as a biomarker for cardiac allograft vasculopathy: Evaluation of diagnostic potential and clinical utility. *Clin Transplant*. 38(1):e15168. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37882497/

- Prospective cohort study of 156 adult heart transplant recipients investigating the relationship between measurements of plasma high-sensitivity troponin I levels (hsTnI) and concurrent CAV grade
- Troponin I levels were positively correlated with concurrent CAV grade after adjustment for age, age at transplant, sex, BMI, hypertension, diabetes, hyperlipidemia, eGFR, and history of ACR (p=0.16).

Kim JV, et al. (2023). Regulatory T Cell Biomarkers Identify Patients at Risk of Developing Acute Cellular Rejection in the First Year Following Heart Transplantation. Transplantation. 2023 Aug 1;107(8):1810-1819. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37365692/

- Prospective, observational study to determine whether HEARTBiT and TGS could be used together to provide an improved clinical tool for heart transplant care.
- Compared to non-rejection samples, rejection samples showed decrease Treg and increased Tconv-gene expression. The TGS panel discriminated between ACR and non-rejection samples. When TGS was combined with HEARTBiT, it showed improved specificity compared to either model alone.

Goldberg JF, et al. (2023). Selection and Interpretation of Molecular Diagnostics in Heart Transplantation. Circulation. 2023 Aug 22;148(8):679-694. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37603604/

- Review of modern strategies used in management of heart transplant recipients

Richmond ME, et al. (2023). Validation of donor fraction cell-free DNA with biopsy-proven cardiac allograft rejection in children and adults. J Thorac Cardiovasc Surg. 2023 Feb;165(2):460-468.e2. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35643770/

- Prospective, observational cohort study to further describe the association of DF cfDNA with biopsy proven ACR and AMR.
- n=130 adult heart transplant recipients providing 745 samples
- For all patients, DF cfDNA at a threshold of 0.14% had a sensitivity of 67%, a specificity of 79%, a PPV or 34%, and a NPV of 94% with an AUC of 0.78 for detecting rejection.

Knuttgen F, et al. (2022). Graft-derived cell-free DNA as a noninvasive biomarker of cardiac allograft rejection: a cohort study on clinical validity and confounding factors. Transplantation. 106(3):615-622. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33653997/

- Prospective cohort study included 87 patients and 770 serial dd-cfDNA samples drawn at predefined time-points. The study found dd-cfDNA plasma values were significantly associated with cardiac rejection ($p<0.001$). Confounding factors identified included pericardial effusions and improper sampling (e.g. shortly after biopsy) which should be considered when dd-cfDNA is used for rejection diagnoses.

Qian X, et al. (2022). Noninvasive biomarkers in heart transplant: 2020–2021 year in review. Current Opinion in Organ Transplantation. 2022;27(1):7-14. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34939959/

- This article reviewed recent advances in the field of noninvasive biomarkers to detect allograft rejection after heart transplant. Noninvasive biomarkers discussed include donor-derived cell-free DNA (dd-cfDNA), MicroRNAs, high-sensitive cardiac troponin (hs-cTnI), N-terminal pro-brain natriuretic peptide (NTproBNP), donor-specific antibodies (DSAs), and circulating extracellular vesicles (EVs).

Kewcharoen J, et al. (2022). Initiation of noninvasive surveillance for allograft rejection in heart transplant patients > 1 year after transplant. Clin Transplant., 36(3):e14548. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34843112/

- This retrospective cohort study described their use of gene expression profiling (GEP) and dd-cfDNA in 18 heart transplant recipients > 1-year post-transplantation. Among nine endomyocardial biopsies (EMBs) in 7 patients, one sample showed acute cellular rejection grade 2R due to elevations of both GEP and dd-cfDNA. This study showed use of both GEP and dd-cfDNA led to an increased number of EMB in patients > 1-year post-transplantation but with a high false-positive rate.

Agbor-Enoh S, et al. (2021). Cell-Free DNA to Detect Heart Allograft Acute Rejection. Circulation, 143(12):1184–1197. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33435695/

- This was a multicenter, prospective cohort study that recruited heart transplant patients and collected plasma samples with endomyocardial biopsy (EMBx) for %ddcfDNA measurement. They included 171 patients and found that medidan %ddcfDNA levels decayed after surgery and then increased in relation to diagnosis of ACR/AMR. %ddcfDNA had a negative predictive value for rejection of 99% and would have safety eliminated 81% of EMBx. This study found that %ddcfDNA monitoring could have earlier detection than EMBx based monitoring for ACR/AMR.

Castellani C, et al. (2020). Circulating extracellular vesicles as non-invasive biomarker of rejection in heart transplant. The Journal of Heart and Lung Transplantation, 39(10):1136–1148. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32665078/

- This study aimed to investigate differences in plasma derived extracellular vesicles (EVs) surface protein profiles as a biomarker to use in combination with endomyocardial biopsies (EMBx) for diagnosis of rejection. This study found that the concentration of EVs was significantly increased and diameter decreased in patients undergoing rejection. The trend was highly significant for both AMR and ACR. This study concluded that circulating EVs could be a promising new tool to characterize cardiac allograft rejection and be complementary to EMB monitoring.

Zhang X, et al. (2020). Association of vimentin antibody and other non-HLA antibodies with treated antibody mediated rejection in heart transplant recipients. Human Immunology, 81(12):671–674. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33041085/

- This study utilized a selected cohort of patients without HLA DSAs but diagnosed with AMR and found the presence of vimentin antibody that was associated with AMR. Therefore they suggest that heart transplant patients should be examined for non-HLA antibodies as well.

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)

Han J, et al. (2024) HLA sensitization is associated with an increased risk of primary graft dysfunction after heart transplantation. *J Heart Lung Transplant*. 43(3):387-393. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37802261/

- Retrospective study examining 596 HTR from 1/2015 to 12/2019 across two centers to determine the association between pretransplant human leukocyte antigen (HLA) sensitization and the risk of PGD. Univariable logistic modeling showed that peak cPRA-LS for all loci, though more specifically HLA-A, was associated with increased severity of PGD (all loci: OR 1.78, 95%CI: 1.01-1.14, p = 0.025, HLA-A: OR 1.14, 95%CI: 1.03-1.26, p = 0.011).

Han J, et al. (2023). Primary graft dysfunction is associated with development of early cardiac allograft vasculopathy, but not other immune-mediated complications, after heart transplantation. *Transplantation*. 107(7): 1624-1629. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36801852/

- Retrospective single-center study examining 381 HTR from 1/2015 to 7/2020 investigating the association between PGD and development of ACR, de novo DSAs and CAV following transplantation. During the first year following transplantation, there was similar incidence of ACR and development of de novo DSA, but higher incidence of CAV (52.6% v. 24.8%, p = 0.28) in patients with PGD than those without.

Ayer A, et al. (2023) Improved outcomes in severe primary graft dysfunction after heart transplantation following donation after circulatory death compared with donation after brain death. *J Card Fail*. 29(1): 67-75. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36351494/
Keywords: primary graft dysfunction, DCD, DBD

- Single-center retrospective cohort study comparing incidence, severity, and outcomes of patients experiencing PGD after DCD (n=65) compared to DBD (n=394) heart transplantation. DCD HTR were more likely to experience severe, biventricular PGD than DBD (34% v. 23%, p=0.07). However, DCD recipients with severe PGD spent fewer days on mechanical circulatory support and in hospital than similar DBD patients, suggesting patterns of graft dysfunction and recovery may differ between groups.

McCartney S, et al. Healthcare resource utilization and clinical outcomes for adult heart transplant recipients with primary graft dysfunction. *Clin Transplant*. 37(10), e15048. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37363857/

- Single-center retrospective study examining 359 HTR between 7/2013 to 7/2019 and the cost burden of PGD. PGD was associated with a 0.42 increase in z-score of total patient costs (95% CI: 0.22-0.62, p<0.001). Any grade of PGD was associated with a 2.95 increase in odds for a higher cost of transplant (95% CI: 1.94-4.46, p <0.0001).

Smith NF, et al. (2022). Primary graft dysfunction in heart transplant recipients-risk factors and longitudinal outcomes. *ASAIO J*, 68(3):394-401. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34593684/

- Single-center, retrospective cohort study (n=448) investigating primary graft dysfunction (PGD) by applying the ISHLT consensus definition to identify risk factors and long-term outcomes. The incidence of PGD was 16.5% (n = 74). The study found development of PGD is associated with higher 30 day-, 1 year-, and 5 year-mortality (p < 0.0001). Risk factors associated with PGD include prolonged ischemic time and multiple perioperative transfusions.

Jernryd V, et al. (2022). Myocardial injury biomarkers at point of care for early identification of primary graft dysfunction after heart transplantation. *Clinical Transplantation*. 2022;36(2). Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34738670/

- Prospective observational study (n=63) found patients with high CK-MB (>11 ng/ml) had an increased risk for severe primary graft dysfunction (p = 0.037). Similar but non-significant trends were observed for cTnI.

Chinnadurai T, et al. (2022). The Interaction of Amiodarone and Continuous-flow Left Ventricular Assist Device Use in Risk of Severe Primary Graft Dysfunction Following Heart Transplantation. *Transplant Direct*, 8(2):e1281. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35047663/

- Single-center retrospective study (n=243) that evaluated risk factors for severe PGD. Severe PGD was independently associated with amiodarone use and CF-LVAD use, and a higher prevalence was found if both risk factors were present (CF-LVAD-/amiodarone- 1.5%, CF-LVAD-/amiodarone+ 4.5%, CF-LVAD+/amiodarone- 7.1%, CF-LVAD+/amiodarone+ 21.8%; p<0.01). There was no mortality associated with amiodarone discontinuation.

Truby LK, et al. (2021) Proteomic profiling identifies CLEC4C expression as a novel biomarker of primary graft dysfunction after heart transplantation. *J Heart Lung Transplant*. 40(12):1589-1598. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8670564/

- Single-center study from 2016 to 2020 to identify whether pre-transplant levels of circulating proteins on immune activation and inflammation are associated with incidence of primary graft dysfunction (PGD). Adult heart transplant recipients were randomly divided in derivation (n=131) and validation (n=88) sets. Nine proteins were associated with PGD in univariate models in the derivation set. Only CLEC4C, a protein marker of plasmacytoid dendritic cells (pDCs), remained associated with PGD in the validation set. The study concluded that pre-transplantation circulating levels of CLEC4C may identify heart transplant patients at risk for PGD.

Noly PE, et al. (2021). Use of extracorporeal membrane oxygenation for heart graft dysfunction in adults: Incidence, risk factors and outcomes in a multicentric study. *Can J Surg*, 64(6):E567-E577. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8565882/

- Multicenter retrospective cohort study in France and Canada from 1/2003 to 12/2013 investigating predictive risk factors for the need for mechanical circulatory support with VA-ECMO in patients with graft dysfunction.
- In-hospital mortality was higher in patients requiring VA-ECMO (57%) than in patients managed with medication alone (14%) (p = 0.001). Overall survival was lower in the VA-ECMO group at both 1 and 5 years (42% vs. 83%; 40% vs. 78%). Survival was very poor in the delayed VA-ECMO group (12% vs. 60% at 1 year, p <0.001). The incidence of graft dysfunction increased over the course of the study period of ten years from 23% to 41%, and rates of VA-ECMO increased over the study period. However, hospital mortality rate decreased over the study period in all patients.

Nagy A, et al. (2021). Endocrine management and hormone replacement therapy in cardiac donor management: A retrospective observational study. *Transplant Proc*, S0041-1345(21):00696-5. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34756710/

- Single center retrospective observational study in Hungary from 1/2012 to 9/2018 investigating effect of hormone replacement in heart donor on recipient outcomes. Neither central diabetes insipidus nor the use of desmopressin/vasopressin showed an association with PGD. Thyroxine replacement in donors was associated with a significant decrease in PGD development in recipients (p = 0.015). It was also associated with a decrease in 30-day mortality (p = 0.028). The use of thyroxine and methylprednisolone together showed less PGD than thyroxine use alone (p = 0.001 vs. p = 0.006), but there was no significant change in recipient survival when comparing the combination of medications vs. thyroxine alone.

Mehdiani A, et al. (2021). Extracorporeal membrane oxygenation after heart transplantation: Impact of type of cannulation. *Thorac Cardiovasc Surg*, 69(3):263-270. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32035427/

- Single center retrospective cohort study performed in Germany from 10/2010 to 10/2017 to compare peripheral (pECMO) and central (cECMO) cannulation for extracorporeal life support (ECLS) in patients requiring ECMO due to PGD. Weaning of ECMO was successful in 7 of 10 patients in the cECMO group and in 7 of 15 patients in the pECMO group (p = 0.414). There were no significant differences in adverse events, 30-day or 1-year mortality between the two groups.

Lim HS, et al. (2021). Cardiac power output index and severe primary graft dysfunction after heart transplantation. *J Cardiothorac Vasc Anesth*, 35(2):398-403. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32747204/

- Single center retrospective cohort study performed in the United Kingdom from 1/2014 to 12/2019 to determine if cardiac power output index (CPOi) can help predict severe primary graft dysfunction after heart transplant. 22 out of 140 study patients developed severe PGD. These patients had a significantly lower CPOi at time of transplant and at 6 hours after transplant. The study indicated that low CPOi at time of transplant is associated with severe PGD, and further testing of CPOi increases the likelihood that the diagnosis of PGD is accurate.

Loforte A, et al. (2021). Mechanically supported early graft failure after heart transplantation. *Transplant Proc*, 53(1):311-317. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32768287/

- Single center retrospective cohort study (n=499) performed in Italy from 1/2000 to 12/2019 to determine the risk factors for severe early graft failure (EGF) in mechanically supported recipients and the impact of EGF on early and late outcomes after heart transplant. Overall EGF rate was 11.6%. The majority of ECMO use was due to PGD (68.5%), and the remainder of cases needing ECMO were due to secondary graft failure (SGF).
- The EGF group had an early mortality rate of 53.1% compared to 5.5% in the non-EGF group ($p < 0.001$). Independent factors that were associated with EGF were pre-operative transpulmonary gradient >12 mmHg, pre-operative inotropic score >10, and pre-operative ECMO support. A Eurotransplant donor score of 17 or greater was also associated with EGF occurrence. Long-term survival was significantly better in those without EGF (94% at 1 year, 85% at 5 years) compared to those with EGF (36% at 1 year, 28% at 5 years) ($p < 0.001$).

Nakamura Y, et al. (2020). Intraoperative hemoglobin level and primary graft dysfunction in adult heart transplantation. *Gen Thorac Cardiovasc Surg*, 68(11):1260-1269. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32300940/

- Single center retrospective cohort study (n=69) performed in Japan from 2007 to 2016 to determine if serum hemoglobin level at time of transplant impacts the risk of developing PGD after transplant. Mean serum hemoglobin level at time of reperfusion was lower in the PGD group than in the non-PGD group ($p = 0.009$).
- Compared to the non-PGD group, the PGD group had higher transfusion volume ($p = 0.003$), higher in-hospital mortality (25.0 % v. 1.8%, $p < 0.05$), longer post-op intubation time and length of stay in the ICU (106 hours vs. 37 hours intubated; 24 days vs. 5 days in the ICU; $p < 0.0001$), and lower 1-year survival (75% vs. 95.9%, $p = 0.004$).

Urban M, et al. (2020). Impact of temporary mechanical circulatory support for early graft failure on post-heart transplantation outcomes. *Clin Transplant*, 34(11):e14060. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32772397/

- Single center retrospective cohort study performed in the United States from 2007 to 2017 to determine how early post-transplant VA-ECMO or RVAD support impacts post-transplant outcomes. 30-day mortality occurred in 0.4% of the non-MCS group and in 44% of the MCS group. In hospital mortality occurred in 2% of the non-MCS group and in 56% of the MCS group. Patients who received VA ECMO support had a higher in-hospital mortality compared to the patients who received RVAD support (73% vs. 33%, $p = 0.038$). Patients who did not receive MCS had better long-term survival compared to those who received MCS (1-year: 96%, 5-year: 89% vs. 1-year: 40%, 5-year: 22%), though this difference in overall survival was not significant in a multivariate analysis ($p = 0.22$).

Nagy A, et al. (2020). Perioperative low tetraiodothyronine levels and adverse outcomes after heart transplantation: A retrospective, observational study. *J Cardiothorac Vasc Anesth*, 34(10):2648-2654. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32389455/

- Single center retrospective cohort study performed in Hungary from 1/2015 to 12/2019 to determine if perioperative T3 and T4 levels impact post-transplant outcomes. Low T4 levels are associated with increased risk for PGD ($p < 0.001$) and associated with higher 30-day mortality

compared to normal T4 levels. Decreased T3 and T4 levels together are associated with increased risk of PGD (p = 0.008).

Peled Y, et al. (2020). Donor thyroid hormone therapy and heart transplantation outcomes: ISHLT transplant registry analysis. *J Heart Lung Transplant*, 39(10):1070-1078. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32771439/

- Multicenter retrospective cohort study using the International Society for Heart and Lung Transplantation Thoracic Transplant Registry from 1/2006 to 12/2016. The aim of this study was to determine if donor thyroid hormone (DTH) therapy is associated with early graft loss (EGL).
- Of the patients included in the study population, 68.8% had received a heart transplant from a donor who received TH supplementation. Patients in the DTH group had higher rates of EGL compared to the no DTH group (1.6% vs 1.1%, p = 0.015), leading to death or retransplant due to graft failure within 48 hours of transplant. 30-day mortality (4.4% vs 4.5%, p = .608) and 8-year survival (p = 0.14) was not significantly different between the two groups.

Peled Y, et al. (2020). Donor thyroid hormone therapy is associated with an increased risk of graft dysfunction after heart transplantation. *Clin Transplant*, 34(7):e13887. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32367594/

- Single center retrospective cohort study performed in Israel from 8/1997 to 8/2018 to determine if thyroid hormone therapy in donors increases the risk of PGD in recipients after transplant. The donors who received T4 therapy had a higher incidence of PGD compared to the donors who did not receive T4 therapy (57.6% vs. 34.7%, p = 0.022). PGD severity was also worse in donors who received T4 therapy (42% vs. 25% moderate/severe PGD, p = 0.007). If the donor received T4 therapy and methylprednisolone, the incidence of PGD was not significantly different from the non-T4 donors (43% vs 34%, p = 0.341). Recipients of donors who were treated with T4 therapy had a higher usage of inotropes after transplant (54% vs. 35%, p = 0.049). In hospital and 30-day mortality did not significantly differ between the groups.

Peled Y, et al. (2020) Preoperative statin therapy and heart transplantation outcomes. *Annals Thorac Surg*. 110(4):1280-1285. 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).

Nicoara A, et al. (2020). Association between primary graft dysfunction and acute kidney injury after orthotopic heart transplantation – a retrospective, observational cohort study. *Transp Int*, 33(8):887-894. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32299144/

- Multicenter retrospective cohort study derived from UNOS data from 1/2009 to 12/2014 to determine if PGD is a risk factor for post-transplant acute kidney injury (AKI). Development of more severe AKI (stage 2-3) was significantly associated with PGD requiring VAD support, an association that was not present in those who developed no AKI or a less severe AKI (no/stage 1) (22.35% vs. 8.66%, p = 0.001). In a multivariate analysis, independent factors associated with increased risk of developing stage 2-3 AKI included PGD requiring VAD, longer DBD duration, recipient pre-transplant serum creatinine, and recipient gender (male at higher risk).

Nilsson J, et al. (2020). A nonrandomized open-label phase 2 trial of nonischemic heart preservation for human heart transplantation. *Nat Commun*, 11(1):2976. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32532991/

- Prospective, open-label, non-randomized trial performed in Sweden from 4/2017 to 9/2018 to determine if rates of primary graft dysfunction (PGD) were different between donor hearts using non-ischemic heart preservation (NIHP) compared to standard static cold preservation (SCS).
- At 6 months, 100% of the patients in the NIHP group (n = 6) achieved survival without severe PGD at 24 hours, without use of ECMO within 7 days, and without acute cellular rejection (ACR) of grade 2R or greater within 180 days; 72% of the SCS group (n =25) achieved the same outcome.

Hoemann B, et al. (2020). Discontinuing amiodarone treatment prior to heart transplantation lowers incidence of severe primary graft dysfunction. *Clin Transplant*. 34(2):e13779. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31903624/

- Single center retrospective cohort study performed in the United States from 1/2010 to 6/2017 to determine if discontinuing amiodarone before transplant lowers the occurrence of severe PGD. There are 3 groups: Group 1 (N=197) did not receive amiodarone, Group 2 (n=142) received amiodarone continued to time of transplant, and Group 3 (n=42) received amiodarone that was stopped before transplant.
- Only 1 patient (2.4%) in Group 3 was readmitted for new onset atrial fibrillation after amiodarone discontinuation. Difference in severe PGD was significantly different between the three groups: Group 1: 6.6%, Group 2: 25.4%, Group 3: 9.5% ($p < 0.001$). One through four-year survival was not significantly different between the groups.
- Multivariate analysis showed that intraoperative packed red blood cell administration ($p < 0.001$) and amiodarone continued to time of transplant ($p = 0.018$) were risk factors for development of severe PGD. In-hospital mortality was not significantly different between the groups.

Jennings DL, et al. (2017). Pre-cardiac transplant amiodarone use is not associated with postoperative mortality: An updated meta-analysis. *Int J Cardio*l. 236:345-347. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28238350

- Meta-analysis of the available evidence (9 studies, 16,509 patients) 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*. 36(11):1217-1225. 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. Risk factors that predicted non-recovery from P-GD were donor age, recipient diabetes, ischemic time, and post-operative dialysis. 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*. 161(5):1273-1278. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27876282

- Single center retrospective study from 1/2004 to 12/2015 comparing outcomes of patients who were taking amiodarone for at least 120 days pre-transplant versus those who did not take amiodaron pre-transplant. The amiodarone group had fewer ACR events (5% vs 20%, p=0.001) but more PGD (4% vs 0%, p=0.025) than the amiodarone-naïve group, but 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

- SRTR registry study of 11,473 patients who received a heart transplant before age 40 between 1988-2013. 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

- Retrospective study examining the incidence of graft failure and the population-attributable risk of independent risk factors for graft failure amongst HTR from 2004-2012. 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

Batra J, et al (2024). A change of heart: Characteristics and outcomes of multiple cardiac retransplant recipients. *Clin Transplant*. 38(1):e15214. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38078705/

- UNOS registry study between 1/1990-12/2020 of individuals receiving 3rd (N=90) and 4th (N=3) heart transplants. Third heart transplant was associated with significantly higher rates of 1-year and 10-year mortality compared to second and primary heart transplant (1-year: 18% vs 13% vs 9%; 10-year: 59% vs 42% vs 37%). The highest mortality rates were seen in age >60 yo and retransplant due to acute graft failure. Other morbidity markers (CAV, rejection, chronic dialysis, hospitalization for infection) were also higher in the third transplant group.

Malas J, et al (2023). Heart retransplant recipients with renal dysfunction benefit from simultaneous heart-kidney transplantation. *J Heart Lung Transplant*. 42(8):1045-1053. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37098375/

- UNOS registry study between 2005-2020 comparing heart-only retransplantation (N=938) vs heart retransplant with simultaneous kidney transplant (HRT-KT, N=251). The HRT-KT group saw improved 5-year survival (80.5% vs 69.1%), particularly in subgroups with eGFR <45 mL/min/1.73 m^2 at time of retransplant.

Zadikany RH, et al. (2021). Total artificial heart as bridge to cardiac retransplantation. *ASAIO J*, 68(3):e77-e79. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33627614/

- Single center case study performed in the United States from 1/2012 to 6/2017 to review outcomes of 3 patients who received therapy with total artificial heart (TAH) before retransplantation. All 3 patients experienced infections and bleeding complications, and only 1 survived to retransplant discharge.

Zhu Y, et al. (2020). Outcomes after heart retransplantation: A 50-year single-center experience. *J Thorac Cardiovasc Surg*: S0022-5223(20)32145-0. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32798029/

- Single center retrospective cohort study performed in the United States from 1/1968 to 6/2019 evaluating outcomes after retransplantation (n=123) compared to primary transplantation (n=2092).
- Patients were more likely to need post-transplant dialysis compared to those who only received a primary transplant (21.4% vs 8.5%, p = 0.034). Median survival was significantly lower after retransplant (4.6 years vs. 9.9 years; p<0.0001). All of the patients who needed a retransplant within 1 year of primary transplant were due to PGD.

Barghash MH and Pinney SP. (2020). Heart retransplantation: Candidacy, outcomes, and management. *Curr Transplant Rep*, 7(1):12-17. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32435573/

- Review article that summarizes the incidence and epidemiology of retransplantation and discusses the risk factors of poor outcomes after retransplantation. Factors associated with retransplant success include retransplant for CAV, >1 year from primary transplant, and not in critical condition.

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 and factors associated with poorer outcomes versus improved survival

5.7 Heart Failure Etiologies and Management

5.7.1 Cardiomyopathy

Hutt, E., & Desai, M. Y. (2024). Medical Treatment Strategies for Hypertrophic Cardiomyopathy. *The Am J Cardiol*, 212S, S33–S41. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38368034/

- Review article on current management strategies for hypertrophic cardiomyopathy, including newly-approved targeted therapies

Bobbio E, et al. (2022). Short- and long-term outcomes after heart transplantation in cardiac sarcoidosis and giant-cell myocarditis: a systematic review and meta-analysis. *Clin Res Cardiol*, 111(2), 125–140. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34402927/

- Systematic review and meta-analysis of post-heart transplant outcomes in patients with inflammatory cardiomyopathies: cardiac sarcoidosis (CS) and giant cell myocarditis (GCM)
- At 5 years, CS patients had higher post-transplant survival (RR 0.72, 95% CI 0.52-0.91) and lower ACR rates (RR 0.38, 95% CI 0.01-0.72) than non-CS patients. GCM patients had similar 1- and 5-year survival compared to non-GCM patients

Yamada T and Nomura S. (2021). Recent findings related to cardiomyopathy and genetics. *Int J Mol Sci*, 22(22):12522. Retrieved from: https://dx.doi.org/10.3390%2Fijms222212522

- Review summarizing genotype-phenotype correlations, indications for genetic testing, and latest findings on pathogenesis and drug discovery for dilated and hypertrophic cardiomyopathy.

5.7.1.1 Dilated Cardiomyopathy

Heymans S, et al. (2023). Dilated cardiomyopathy: causes, mechanisms, and current and future treatment approaches. *Lancet*. 402(10406), 998-1011. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37716772/

- Seminar article reviewing the epidemiology, pathophysiology, causes, diagnosis, management, and future diagnostic/therapeutic perspectives of dilated cardiomyopathies.

Presume J, et al. (2023). Parameters of the mitral apparatus in patients with ischemic and non-ischemic dilated cardiomyopathy. *J Int Med Res*. 51(12):3000605231218645. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10754024/

- Despite the lack of valve disease, mitral regurgitation can occur secondary to DCM. This review article explores the anatomy and pathophysiology behind this change.

Feng J, et al. (2023). Prognostic value of QRS duration in patients with dilated cardiomyopathy according to left ventricular ejection fraction. *Cardiovasc*. 24(12), 362. Retrieved from: https://www.imrpress.com/journal/RCM/24/12/10.31083/j.rcm2412362/htm

- This prospective, observational, single center study sought to describe prognostic role of QRS duration (QRSd) in patients with DCM when stratified by ejection fraction. Of the 633 patients included, 47.7% had an LVEF of 30-50% and 35.7% had a QRSd ≥120 ms.
- Overall, QRSd ≥ 120 ms was associated with an increased risk of the primary composite outcome of death, heart transplantation, and rehospitalization for worsening heart failure (HR 1.65 CI 1.29-2.11, p<0.001) and no significant interaction was observed on LVEF stratification (p =0.067).

Cinq-Mars A, et al. (2021). Heavy burden of toxic dilated cardiomyopathy among young adults: a retrospective study and review of the literature. *Can J Cardiol*, S0829=8-282X(21)00823-0. Retrieved from: https://doi.org/10.1016/j.cjca.2021.11.002

- Single center retrospective cohort study in Canada between 1/2003 to 8/2019 evaluating outcomes in patients under 65 years with toxic dilated cardiomyopathy (TCM). Of the 201 patients with idiopathic dilated cardiomyopathy, 38 were suspected to be due to TDM caused by use of

amphetamine, cocaine, anabolic steroids, and/or energy drinks. After GDMT, 27 patients had event-free survival at the end of the follow-up period and 23 had an LVEF>40%. Seven patients required LVAD support and one required ECMO as a bridge to transplantation.

Ebbesen MN, et al. (2021). Rate of heart failure following atrial fibrillation according to presence of family history of dilated cardiomyopathy or heart failure: a nationwide study. *J Am Heart Assoc*, 10(22):e021286. Retrieved from: https://doi.org/10.1161/jaha.120.021286

- Patients diagnosed with atrial fibrillation from 2005-2015 were identified through Danish nationwide registries and followed for 5 years to assess the rate of development of heart failure and determine if having first-degree relatives with HF or DCM was a risk factor. A total of 10,605 patients were included, with 17% having one or more family member(s) with HF or DCM. A first-degree relative was associated with an increased risk of HF or death (adjusted HR 1.36 [95% CI, 1.12-1.64]). Familial HF/DCM was not significantly associated with an increased 5-year risk of death (adjusted HR, 0.80 [95% CI, 0.46–1.39]).

Moeinafshar A, et al. (2021). Diagnostic biomarkers of dilated cardiomyopathy. *Immunobiology*, 226(6):152153. Retrieved from: https://doi.org/10.1016/j.imbio.2021.152153

- Review article that discusses the characteristics, epidemiology, etiology, and manifestations of DCM. It discusses the most important biomarkers and genetic mutations for diagnosing DCM.

Chen Y, et al. (2021). Outcomes of spironolactone withdrawal in dilated cardiomyopathy with improved ejection fraction. *Front Cardiovasc Med*, 8:725399. Retrieved from: https://doi.org/10.3389/fcvm.2021.725399

- This single center prospective cohort study performed in China from 6/2016 to 6/2017 aimed to determine the outcomes of spironolactone withdrawal in patients with improved LVEF in remission for DCM (n=70).
- Fifty-eight percent of the withdrawal group (n=23) and 13% of the continuation group (n=4) experienced relapse in DCM, leading to a relative risk for relapse after spironolactone withdrawal of 4.31, 95% CI 1.67-11.11 ($p < 0.001$). More patients in the withdrawal group experienced aggravation of HF symptoms compared to the continuation group (RR 3.18, 95% CI 1.19-8.47; $p = 0.008$). The continuation group experienced continued ventricular remodeling, whereas the withdrawal group did not see any further remodeling after withdrawal.

Ivanov B, et al. (2021). Impact of ischaemic and dilated cardiomyopathy on short-term and long-term survival after ventricular assist device implantation: a single-centre experience. *Heart Lung Circ*, S1443-9506(21)01232-4. Retrieved from: https://doi.org/10.1016/j.hlc.2021.08.017

- This single center retrospective cohort study performed in Germany from 2/2010 to 12/2020 aimed to determine the outcomes after LVAD implantation in patients with ICM (n=36) and DCM (n=24). HeartWare HVAD was used in 47 patients with no significant differences based on type of cardiomyopathy (p=0.542). Patients with ICM had a higher number of additional cardiac procedures during LVAD implantation (36% ICM vs. 12% DCM, $p = 0.052$). Post-op milrinone was significantly different between the groups (0.2 mcg/kg/min ICM vs. 0.25 mcg/kg/min DCM, $p < 0.001$). In-hospital mortality and hospital length of stay were not significantly between the groups ($p = 0.206$, $p = 0.349$).

Enzan N, et al. (2021). The use of angiotensin-converting enzyme inhibitors or angiotensin ii receptor blockers is associated with the recovered ejection fraction in patients with dilated cardiomyopathy. *Int Heart J*, 62(4):801-810. Retrieved from: https://doi.org/10.1536/ihj.20-671

- This multicenter prospective cohort performed in Japan from 2003 to 2014 aimed to determine if ACEi/ARB use was associated with HF with recovered EF on patients with DCM. The prevalence of LVEF of 40% or greater at 3 years in the ACEi/ARB group (57.0%) was higher than in the non-ACEi/ARB group (49.3%) ($p = 0.002$).

Enzan N, et al. (2021). Beta-blocker use is associated with prevention of left ventricular remodeling in recovered dilated cardiomyopathy. *J Am Heart Association*, 10(12):e019240. Retrieved from: https://doi.org/10.1161/jaha.120.019240

- This multicenter prospective case-matched study performed in Japan from 2003 to 2014 aimed to determine the outcomes of beta-blockers on LVEF in patients with recovered DCM. A decrease in LVEF >10% was less common in the beta-blocker group compared to the non-beta-blocker group (19.6% vs 24.0%, p=0.013). An increase in LV diastolic diameter was less common in the beta-blocker group compared to the non-beta-blocker group (11.7% vs 15.7%, p = 0.008) and the beta-blocker group had less deterioration to LVEF < 40% (24.2% vs 30.4%, p=0.003).

Kim HM, et al. (2021). Beneficial effect of left ventricular remodeling after early change of sacubitril/valsartan in patients with non-ischemic dilated cardiomyopathy. *Medicina (Kaunas)*, 57(5):416. Retrieved from: https://doi.org/10.3390/medicina57050416

- This single center retrospective cohort study performed in South Korea from January 2009 to November 2019 aimed to determine if an early switch from ACEi/ARB to sacubitril/valsartan improved LVEF in patients with DCM.
- In patients who switched to sacubitril/valsartan within 60 days, the increase in LVEF and decrease in LV end-systolic diameter were more significant than those who switched later (p = 0.05, p = 0.005) and those who continued ACEi/ARB therapy (p = 0.036, p = 0.023). There were no significant differences in clinical outcomes between the groups with regard to early/late switch to sacubitril/valsartan.

Fu L, et al. (2020). The impact of atorvastatin on cardiac performance for dilated cardiomyopathy: a meta-analysis of randomized controlled studies. *Heart Surg Forum*, 23(3):E329-E334. Retrieved from: https://doi.org/10.1532/hsf.2787

- A systematic review and meta-analysis of literature through February 2019 was performed to determine the influence of atorvastatin on cardiac performance in patients with dilated cardiomyopathy. The analysis found that LVEF was significantly increased in patients on atorvastatin (p < 0.00001). In addition, atorvastatin was associated with a significantly improved positive impact on 6-minute walk test (p= 0.003).

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

- This prospective, double-blind study sought to determine differences in dyssynchrony, LV volume, and LVEF between carvedilol and metoprolol. Compared with metoprolol, carvedilol was associated with greater reduction in LV end diastolic volume (p=0.03), increase in LVEF (p=0.02), and improvement in inter-ventricular dyssynchrony (p=0.03). 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

Medarametla G, et al. (2023). Cardiac amyloidosis: evolving pathogenesis, multimodal diagnostics, and principles of treatment. *EXCLI J*. 22:781-808. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37720240/

- This review discusses diagnosis, clinical features, and management strategies for cardiac amyloidosis.

Patel R, et al. (2023). Cardiac sarcoidosis: a literature review of current recommendations on diagnosis and management. *Cureus*. 15(7):e41451. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37546036/

- This review discusses diagnosis, clinical features, and management strategies for cardiac sarcoidosis.

Wang H, et al. (2023). Prevalence and impact of arrhythmia on outcomes in restrictive cardiomyopathy—a report from the Beijing municipal health commission information center (BMHCIC) database. *J Clin Med*. 12(3):1236. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9917641/

- This retrospective cohort study of 1148 patients with RCM identified through the BMHCIC database sought to determine the impact of arrhythmias on prognosis and outcomes of patients with RCM.
- Atrial fibrillation was associated with an increased risk of stroke and systemic embolism (adjusted HR 1.37 CI 1.02-1.83, p=0.04) while ventricular tachycardia and bradyarrhythmia were not (aHR 1.41 CI 1.00-1.99, p=0.05 and aHR 1.01 CI 0.78-1.30, p=0.97, respectively). Over a median of 4.8 years, VT had the greatest risk of death (aHR 2.07 CI 1.19-3.59, p=0.01) while AF was associated with reduced risk of death (aHR 0.51 CI 0.31-0.83, p=0.01) and bradyarrhythmia had no impact (aHF 1.13 CI 0.71-1.79, p=0.62).

Wiefels C, et al. (2022). Investigating the treatment phenotypes of cardiac sarcoidosis: a prospective cohort study. *Am Heart J Plus*. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37441681/

- This prospective study of 21 patients with cardiac sarcoidosis sought to assess response to corticosteroids and the incidence of relapse after one-year.
- Nineteen (90.5%) initially responded to prednisone therapy (≥ 25% reduction in LV standardized uptake value). At 1 year of follow up, 12 (63.1%) patients relapsed after stopping prednisone. Those that did not require chronic therapy (7/19) were classified as acute phenotype and the other 12 as chronic phenotypes.

Jackson KC, et al. (2022). Heart transplantation outcomes in cardiac sarcoidosis. *J Heart Lung Transplant*, 41(1):113-122. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34756511/

- This retrospective analysis using UNOS database information examined outcomes in patients with cardiac sarcoidosis (n=227). There was no difference in survival, graft failure, hospitalizations for infection, and post-transplant malignancy between patients with cardiac sarcoidosis and non-cardiac sarcoidosis. Patients with cardiac sarcoidosis had lower odds of rejection (OR 0.558, CI 0.315-0.985, p=0.0444).

McGoldrick MT, et al. (2021). Long-term survival after heart transplantation for cardiac sarcoidosis. *J Card Surg*, 36(11):4247-4255. Retrieved from: https://doi.org/10.1111/jocs.15783

- This multicenter retrospective cohort study using OPTN database information evaluated post-transplant survival in 289 patients with restrictive cardiomyopathy due to cardiac sarcoidosis (RCM-Sarcoidosis).
- One year survival between the RCM-Sarcoidosis and non-RCM groups were similar (91.6% vs. 89.7%, p = 0.306). Five year and 10 year survival were significantly higher in the RCM-sarcoidosis group compared to the non-RCM group (5-year: 87.7% vs. 77.2%, p = 0.004; 10-year: 73.4% vs. 59.5%, p = 0.002). For those with RCM due to other causes, 1-, 5-, and 10-year survival were all significantly worse compared to the non-RCM group (86.3% vs 89.7%, 72.0% vs 77.2%, and 53.9% vs 59.5.

Sreenivasan J, et al. (2021). Left ventricular assist device implantation in hypertrophic and restrictive cardiomyopathy: a systematic review. *ASAIO J*, 67(3):239-244. Retrieved from: https://doi.org/10.1097/mat.0000000000001238

- A systematic review of literature through May 2019 was performed to evaluate clinical outcomes of patients with LVAD due to hypertrophic cardiomyopathy (HCM) or restrictive cardiomyopathy (RCM) compared to those with dilated cardiomyopathy (DCM) or ischemic cardiomyopathy (ICM).
- Perioperative and short-term mortality were significantly higher in the HCM/RCM group (14.0%) compared to the DCM/ICM group (9.0%) ($p < 0.001$). Post-op RV failure requiring inotrope support was higher in the HCM/RCM group compared to the DCM/ICM group (50.0% vs. 21.0%, $p < 0.001$). The HCM/RCM group had significantly more post-op complications: infection 15.5%

vs. 11.2%, bleeding 40.2% vs. 12.5%, acute renal failure 15.0% vs. 5.1%, arrhythmias 18.0% vs. 7.7%, stroke 5.0% vs. 2.4% (all p < 0.001).

Michelis KC, et al. (2020). Durable mechanical circulatory support in patients with amyloid cardiomyopathy: insights from INTERMACS. *Circ Heart Fail*, 13(12):e007931. Retrieved from: https://doi.org/10.1161/circheartfailure.120.007931

- Multicenter retrospective cohort study from the INTERMACS database aimed to determine the clinical outcomes of mechanical circulatory support (MCS) in patients with amyloid cardiomyopathy (ACM) [n=46] compared to dilated cardiomyopathy (DCM) [n=19,921] and non-amyloid restrictive cardiomyopathy (RCM) [n=248].
- Patients with ACM had a higher mortality with heart transplant (p=0.014) compared to those with DCM or non-amyloid RCM. This was consistent for patients requiring LVAD MCS (p<0.001) but no difference in mortality was seen between patients requiring biventricular MCS (p=0.23). ACM was associated with a 2.5-fold increased risk of death compared to DCM (p < 0.001). The ACM group also saw more major bleeding (p= 0.005), neurological dysfunction (p = 0.006), hemorrhagic CVA (p = 0.006), and renal dysfunction (p < 0.001) compared to DCM and non-amyloid RCM groups

Barrett CD, et al. (2020). Outcomes in Patients With Cardiac Amyloidosis Undergoing Heart Transplantation. *JACC Heart Fail*, 8(6):461-468. Retrieved from: *https://doi.org/10.1016/j.jchf.2019.12.013*

- Single center retrospective cohort study in the United States aimed to evaluate outcomes of 31 patients with cardiac amyloidosis that underwent heart transplantation compared to those without cardiac amyloidosis. There were no significant differences in post-operative bleeding, renal failure, infection, rejection, malignancy, or mortality between the AL amyloidosis group (n=13) and the ATTR amyloidosis group (n=18). There was no significant difference in survival between amyloid and non-amyloid cardiomyopathy patients who received a transplant (p=0.229).

5.7.1.3 Infectious Cardiomyopathy

Ramos-Rincon JM, et al. (2023). Cytokine profile levels and their relationship with parasitemia and cardiomyopathy in people with Chagas disease in Spain. A prospective observational study. *Parasitol Res*. 123(1):66. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38133693/

- This prospective observational study of 58 patients aimed to describe serum cytokine profiles of chronic *Trypanosoma cruzi* infection and evaluate its relationship with Chagas cardiomyopathy. Seventeen (29.3%) patients had positive RT-PCRs and they had significantly higher median levels of IL-4 (p=0.031), IL-6 (p=0.021), TNF-α (p=0.003), and IL-17A (p=0.043). Those with cardiac involvement (n=14) had a higher median concentration of IL-5 (p=0.014).

Puerta C, et al. (2022). *Trypanosoma cruzi*-specific CD8+ T cells and other immunological hallmarks in chronic Chagas Cardiomyopathy: Two decades of research. *Front Cell Infect Microbiol* 12:1075717. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36683674/

- This article summarizes one group's experience with research to determine biomarkers for disease progress evaluation, treatment monitoring, and/or drug targets. Based on their findings, potential markers are the TcTLE peptide, use of CD8+ T cell response quality, and the use of memory stem cells.

Papamanoli A, et al. (2022). Human immunodeficiency virus infection – associated cardiomyopathy and heart failure. *J Pers Med* 12(11):1760. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36573732/

- This review article explores the multifactorial pathophysiology of HIV-related cardiomyopathy, the role certain antiretroviral therapies may play, and treatment strategies.

Schultheiss HP, et al. (2021). Viral myocarditis-from pathophysiology to treatment. *J Clin Med*, 10(22):5240. Retrieved from: https://doi.org/10.3390/jcm10225240

- Review article that discusses the pathophysiology, diagnosis, and treatment of viral myocarditis.

Echeverría LE, et al. (2021). Survival after heart transplantation for Chagas cardiomyopathy using a conventional protocol: A 10-year experience in a single center. *Transpl Infect Dis*, 23(4):e13549. Retrieved from: https://doi.org/10.1111/tid.13549

- Single center retrospective cohort study describing the outcomes of 43 patients with Chagas cardiomyopathy (CCM) who underwent heart transplant. Benznidazole prophylaxis and RT-PCR follow up was not used. Chagas' disease reactivation was considered based on microscopic examination or positive immunochemistry in tissue samples.
- One-year survival was 85.87% and 5-year survival was 74.67%, with the most common cause being infection (6/10). *T. cruzi* reactivation was detected in 3 patients (2 with neurological involvement, one with cardiac involvement) and all 3 received treatment with benznidazole. Twenty-six (60.46%) patients experienced at least one rejection, with 13 of them requiring pharmacological treatment.

Holanda MT, et al. (2021). Effects of selenium treatment on cardiac function in Chagas heart disease: Results from the STCC randomized Trial. *EClinicalMedicine*, 40:101105. Retrieved from: https://doi.org/10.1016/j.eclinm.2021.101105

- Single center, prospective, double-blinded, placebo-controlled, phase-3 randomized controlled trial performed in Brazil to determine the safety and efficacy of selenium treatment in chronic Chagas cardiomyopathy (CCC). Sixty-six patients were randomized to receive selenium or placebo for one year.
- No significant differences between LVEF changes were observed at 6 months (-1.4% vs -2.3%, p=0.51) or at 12 months (-1.1% vs -3.3%, p=0.23).There were no significant differences in CCC staging changes between the two groups at 12 months (p=0.25). There were no significant differences in adverse drug reactions between the selenium and placebo groups (p = 0.84).

Benatti RD, et al. (2017). Heart transplantation for Chagas cardiomyopathy. *J Heart Lung Transplant*. 36(6):597-603. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28284779\

- Review article discussing considerations for heart transplant in the setting of Chagas cardiomyopathy and complications in the post-transplant setting.

5.7.1.4 Peripartum Cardiomyopathy

Arany Z. (2024). Peripartum Cardiomyopathy. *N Engl J Med*, 390(2), 154–164. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38197818/

- A review of peripartum cardiomyopathy that describes its epidemiology, pathophysiology, risk factors, diagnosis, and management through different stages of pregnancy.

Imran T, et al. (2024). Clinical predictors of right ventricular dysfunction and association with adverse outcomes in peripartum cardiomyopathy. *ESC Heart Fail*. 11(1), 422-432. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38030384/

- Multi-center retrospective cohort study aimed to determine the outcomes of patients with PPCM (n= 229). The primary composite outcome (need for ECMO, VAD implantation, transplantation, death, or recurrent heart failure hospitalization) was observed in 58 (25%) patients. RV dysfunction on presentation was associated with an increased risk of the composite outcome (multivariate HR 3.21 CI 1.11-9.28). Positive predictors for RV dysfunction were: African ancestry (OR 2.02 CI 1.07-3.82) and familial history of cardiomyopathy (OR 3.30 CI 1.39-7.84).

Jackson A, et al. (2023). A 20-year population study of peripartum cardiomyopathy. *Eur Heart J*. 44(48):5128-5141. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37804234/

- This retrospective, observational study of 225 women with PPCM sought to identify risk factors for development of PPCM. The composite end point of all-cause death, mechanical circulatory support, or cardiac transplantation occurred in 14% of patients with PPCM. Compared to paired controls, patients with PPCM were more likely to have BMI >30 kg/m^2 (OR 1.47 CI 1.02-2.14),

multiple gestation (OR 3.21 CI 1.45-7.13), pre-eclampsia (OR 3.22 CI 1.53-6.81), and pregnancy-induced hypertension (OR 2.66 CI 1.58-4.45). The overall incidence of PPCM was 1 in 4950 deliveries.

Sanigra KJ, et al. (2023). Successful management of peripartum cardiomyopathy in a Kenyan setting: a case series. *Pan Afr Med J*. 28:44:150. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37396700/

- Case series of 5 patients with peripartum cardiomyopathy and severely reduced ejection fractions. All 5 cases recovered with medication therapy and did not require transplantation. Commonly used medications were furosemide, digoxin, spironolactone, and bromocriptine. All patients also received antibiotics.

Kwon JH, et al. (2022). Heart transplantation for peripartum cardiomyopathy: outcomes over three decades. *Ann Thorac Surg*, S0003-4975(22)00066-2. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35085525/

- Retrospective analysis using UNOS database evaluating trends and outcomes of patients undergoing heart transplantation for peripartum cardiomyopathy (PPCM, n=809).
- PPCM was associated with significantly elevated one-year post-transplant mortality compared to non-ischemic cardiomyopathy (HR 1.28, CI 1.11-1.69, p=0.004). This remained true for 5- and 10-year survival (66.5% and 49% vs 74.3% and 56%) until the survival curves crossed at 14 years post-transplant. Those with PPCM transplanted between 2010-2020 had better outcomes than previous eras (HR 0.56 CI 0.32-0.97, p=0.39).

Badianyama M, et al. (2021). A systematic review of the utility of bromocriptine in acute peripartum cardiomyopathy. *Cureus*, 13(9):e18248. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8475739/pdf/cureus-0013-00000018248.pdf

- A systematic review aiming to describe the safety and efficacy of combining bromocriptine with conventional HF treatment in 263 patients with PPCM. Mean LVEF was higher in patients on bromocriptine therapy (58% vs. 36%, p = 0.0007; 49.9 vs 40.9, p = 0.001) as reported in two studies. Another study reported more patients with improved LVEF on bromocriptine vs no bromocriptine (92% vs 72%). In two studies, LVEF was improved by a mean difference of 11.37% and 15.14% in the bromocriptine groups (p = 0.001 and p = 0.0006, respectively). Of the studies reporting deaths, bromocriptine had a lower incidence of death at 6 months.

Djordjevic I, et al. (2021). The outcome of patients with peripartum cardiomyopathy and consecutive implantation of a left ventricular assist device. *J Card Surg*, 36(8):2651-2657. Retrieved from: https://doi.org/10.1111/jocs.15598

- This multicenter retrospective cohort study from the EUROMACS database aimed to determine the outcomes of patients with LVAD due to PCCM (n=16). LVAD was used as a bridge to transplant in 14 (69%) patients and as a bridge to recovery in 2 (13%) patients. Follow-up data was available for 15 patients. Six (40%) patients were transplanted, 3 (20%) patients were weaned off of LVAD support, and 4 (27%) remained on LVAD support through the study. The remaining 2 patients died within the first year, one during the hospital admission.

Karaye KM, et al. (2020). Selenium supplementation in patients with peripartum cardiomyopathy: A proof-of-concept trial. *BMC Cardiovasc Disord*, 20(1):457. Retrieved from: https://doi.org/10.1186/s12872-020-01739-z

- Open-label randomized controlled trial performed in Nigeria to evaluate the efficacy and safety of selenium in patients with PPCM and selenium deficiency. One hundred patients were randomized to receive selenium for 3 months or nothing.
- Over a median of 19 months, the primary outcome of persistent HF symptoms, unrecovered LV systolic function (LVEF<55%), or death from any cause was not different between the two groups (HR 0.69, CI 0.43-1.09, p=0.137). One stratification, persistence of HF symptoms was less common in the selenium group (HR 0.53, CI 0.30-0.93, p=0.006). No serious adverse effects were reported.

Achmad C, et al. (2020). T-peak to T-end improvements after beta-blocker administration in peripartum cardiomyopathy patients. *Cardiol Res*, 11(3):185-191. Retrieved from: https://doi.org/10.14740/cr1053

- A single center prospective cohort study of female patients with PPCM performed in Indonesia aiming to determine if beta-blocker therapy can improve T-peak to T- end (TPTE) interval to decrease outcomes of sudden cardiac death. After 6 months of beta-blocker therapy, mean LVEF improved from 32.24% to 58.26% ($p<0.001$) and mean TPTE was reduced from 123.7 ms to 98.7 ms ($p<0.001$).

Sinkey RG, et al. (2020). Racial disparities in peripartum cardiomyopathy: eighteen years of observations. *J Matern Fetal Neonatal Med*, 1-8: Retrieved from: https://doi.org/10.1080/14767058.2020.1773784

- A single center retrospective cohort study performed in the United States aiming to evaluate outcomes in patients with PPCM of different races to determine if there were any disparities between groups. A total of 95 women (46 identifying as Black and 49 identifying as White) were included. Almost all diagnoses of PPCM were post-partum (95.4% in black women, 93% in white women, $p = 0.11$) and EF at diagnosis was not different (26.8% vs 28.7%, $p=0.04$). At 6-12 months postpartum, black women were more likely to have LVEF <35% ($p<0.01$) and were less likely to recover after subsequent pregnancies (37.5% vs 55%, $p=0.02$). Medication use (DMT) was similar between the groups, although black women were more likely to have emergency room visits, inpatient admissions, and ICU admissions ($p < 0.01$, $p = 0.01$, and $p = 0.005$).

Westhoff-Bleck, M. et al (2013). Cardiovascular disorders in pregnancy: diagnosis and management. *Best Pract Res Clin Obstet Gynaecol*, 27, 821-834. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23932772

- Review article discussing the pathophysiology, diagnosis, and treatment of cardiovascular disorders during pregnancy, including peri-partum cardiomyopathy.

Rasmusson, KD (2007). Long-term outcomes of cardiac transplantation for peri-partum cardiomyopathy: a multi-institutional 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 and females heart transplant recipients with idiopathic dilated cardiomyopathy.
- Risk of rejection was greater for the PPCM group compared to males (RR 1.4, $P<0.0001$) and females without previous pregnancy (RR 1.4, $p=0.04$). No difference in risk of rejection was seen compared to females with previous pregnancy (RR 0.9, $p=0.4$). Long-term survival for PPCM recipients was comparable to males ($p=0.09$) and improved compared to other females ($p=0.07$ compared to those with previous pregnancy and $p=0.05$ compared to those without previous pregnancy).

5.7.1.5 Right Ventricular Cardiomyopathy

Al-Aidarous S, et al. (2024). Management of arrhythmogenic right ventricular cardiomyopathy. *Heart*. 110(3):156-162. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37433658/

- Review article discussing the treatment options for ventricular arrhythmias in ARVC. Medications discussed include beta blockers, amiodarone, and flecainide. Non-pharmacologic treatments include catheter ablation.

Tu B, et al. (2021). Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers: antiarrhythmic drug for arrhythmogenic right ventricular cardiomyopathy. *Front Cardiovasc Med*, 8:769138. Retrieved from: https://doi.org/10.3389/fcvm.2021.769138

- A single center retrospective cohort study of 311 patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) performed in China aimed to determine if the use of ACEi/ARB therapy (n=113) impacts disease progression.

- Those receiving ACEi/ARB therapy had a slower decline tricuspid annular plane systolic excursion (TAPSE) than those not receiving ACEi/ARB therapy (0.24 mm/year vs 0.61 mm/year, p<0.001). ACEi/ARB therapy was associated with a reduced risk of life-threatening ventricular arrhythmias (55.8% vs 71.2%, adjusted HR 0.71, CI 0.52-0.96, p=0.031) and reduced risk of sustained VT (53.5% vs. 63.8%, p = 0.017).

Ren J, et al. (2020). Plasma testosterone and arrhythmic events in male patients with arrhythmogenic right ventricular cardiomyopathy. *ESC Heart Fail*, 7(4):1547-1559. Retrieved from: https://doi.org/10.1002/ehf2.12704

- This single center retrospective cohort study of 195 patients (99 patients with ARVC, 96 control) performed in China sought to determine if testosterone levels could predict major cardiac events in patients with ARVC.
- Male patients with ARVC (n=68) had significantly higher median levels of total testosterone compared to those without ARVC (n=61) (6.390 ng/mL vs 3.617 ng/mL, p<0.0001). In the follow-up period, those that experienced malignant arrhythmias (n=22) had higher medial total testosterone levels than those that did not (n=25) (9.034 ng/mL vs 4.633 ng/mL, p<0.0001). Cox regression analysis determined that the level of plasma total testosterone was an independent predictor of malignant arrhythmic events (HR 1.325, CI 1.171-1.498, p<0.001). No difference was observed in female patients with or without ARVC (p>0.9999).

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

Sicim H, et al. (2024). Determinants of survival following heart transplantation in adults with congenital heart disease. *J Cardiothorac Surg.* 19(1):83. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38336724/

- UNOS registry study of 35,592 heart transplants from 1/2000 to 9/2018 comparing characteristics and outcomes for ICM, NICM, and ACHD. ACHD patients had higher in-hospital mortality compared to ICM and NICM (HR 0.54; 0.46, both p<0.001), but better long-term conditional survival after censoring for hospital deaths (p<0.001). Factors associated with increased mortality were history of cerebrovascular disease or malignancy, pre-transplant biventricular support, post-operative stroke, and post-operative dialysis.

Batsis M, et al. (2021). Association of Digoxin With Preserved Echocardiographic Indices in the Interstage Period: A Possible Mechanism to Explain Improved Survival? *J Am Heart Assoc*, 10(23):e021443. Retrieved from: https://doi.org/10.1161/jaha.121.021443

- A multicenter retrospective cohort study performed in the United States from 2005 to 2008 evaluating the effect of digoxin on RV indices post stage 1 palliation in infants with single ventricle congenital heart disease. After the Norwood procedure, there were no statistical differences between the RV end-diastolic volume, RV end-systolic volume, or ejection fraction between the digoxin and non-digoxin groups. The authors concluded that digoxin use during the interstage period is associated with better preservation of RV volume and tricuspid valve measurements leading to less adverse remodeling of the single ventricle. These findings suggest a possible mechanism of action explaining digoxin's survival benefit during the interstage period.

Donovan DJ, et al. (2021). Association between homograft tissue exposure and allosensitization prior to heart transplant in patients with congenital heart disease. *Pediatr Transplant*, e14201. Retrieved from: https://doi.org/10.1111/petr.14201

- A single center retrospective cohort study performed in the United States from 1/2011 to 3/2018. The aim of this study was to determine the association between pre-sensitization prior to heart

transplant and exposure to homograft tissue in patients with congenital heart disease. Patients who received homografts before transplant were more likely to be pre-sensitized (defined by PRA >10%) (OR=7.31, p = 0.007), and to have developed any anti-HLA antibody at various levels, >0 (OR = 4.52, p = .034), >2000 (OR = 8.59, p = .003), and >6000 (OR=8.50, p=0.004). Patients who were pre-sensitized were more likely to have longer exposure to homograft tissue (9.80 vs. 4.96 years, p = 0.025).

Assenza GE, et al. (2021). AHA/ACC vs ESC Guidelines for Management of Adults With Congenital Heart Disease: JACC Guideline Comparison. *J Am Coll Cardiol*, 78(19):1904-1918. Retrieved from: https://doi.org/10.016/j.jacc.2021.09.010

- A review article summarizing and comparing/contrasting the AHA/ACC and ESC guidelines for adult congenital heart disease.

de la Rosa AL, et al. (2021). Advanced heart failure and heart transplantation in adult congenital heart disease in the current area. *Clin Transplant*, 35(11):e14451. Retrieved from: https://doi.org/10.1111/ctr.14451

- A single center retrospective cohort study performed in the United States from 1/2010 12/2020 evaluating outcomes in patients transplanted for adult congenital heart disease (ACHD). The rates of desensitization were not statistically significant between the ACHD and non-ACHD groups (21.1% vs. 13.2%, p = 0.46). Within the first year of transplant, patients with ACHD were more likely to be treated for ACR (21.1% vs. 15.8%, p = 0.010) and AMR (15.8% vs. 10.5%, p = 0.033). Mortality at 30-days, at 1-year, and at median follow-up of 3.3. years were not significant between the groups (p = 0.26, p = 0.21, p = 0.36, respectively).

Hong KN, et al. (2021). Cardiac Transplantation in Danon Disease. *J Card Fail*, S1071-9164(21)00466-8. Retrieved from: https://doi.org/10.1016/j.cardfail.2021.11.007

- Danon disease is an X-linked dominant mutation that causes severe cardiomyopathy, which is often fatal without heart transplant. A multicenter retrospective study performed in Spain, Italy, and the United States from 12/1985 to 5/2020 aimed to determine post-transplant outcomes in patients with Danon disease (DD) who received a heart transplant. Five-year graft survival was 87.1%. In patients who survived to discharge there was one episode (2.7%) of antibody-mediated rejection, and 7 episodes (19%) of acute cellular rejection.

Huang ST, et al. (2021). Effect of postoperative administration of inhaled nitric oxide combined with high-frequency oscillatory ventilation in infants with acute hypoxemic respiratory failure and pulmonary hypertension after congenital heart surgery: A retrospective cohort study. *J Card Surg*. 1-7. Retrieved from: https://doi.org/10.1111/jocs.16163

- A single center retrospective cohort study performed in China from 1/2020 to 3/2021 determining the impact of inhaled nitric oxide (iNO) combined with high-frequency oscillatory ventilation (HFOV) in patients with acute hypoxemic respiratory failure (AHRF) and pulmonary hypertension (PH) after congenital heart surgery. The oxygenation index (OI) in patients with HFOV and iNO was improved more significantly than in the HFOV group at 6, 12, 24, and 48 hours (p = 0.046, p = 0.034, p = 0.048, and p = 0.046, respectively). PaO_2 was significantly better at 6 and 12 hours in the HFOV and iNO group vs. HFOV group (p = 0.049 and p = 0.047, respectively). The HFOV group had significantly longer duration of mechanical ventilation 7.0 days vs. 5.6 days). ICU length of stay was shorter in the HFOV and iNO group (9.9 days vs. 12.8 days). Hospital length of stay was not significantly different between the groups.

Kainuma A, et al. (2021). Changes in waitlist and posttransplant outcomes in patients with adult congenital heart disease after the new heart transplant allocation system. *Clin Transplant*, 35(11):e14458. Retrieved from: https://doi.org/10.1111/ctr.14458

- A multicenter retrospective cohort study derived from the UNOS database from 1/2010 to 3/2020. The purpose of this study was to determine waitlist and post-transplant outcomes in adult patients with CHD. The allocation policy changed in October 2018 awarding an exception status to patients with ACHD because these patients were previously the lowest priority for heart transplant. There were no significant differences in the before policy change vs. the after policy

change with regards to early complications or 1-year survival (p = 0.791). Compared to patients waitlisted in the pre-policy change era, those waitlisted in the post policy change era were more likely to receive transplants (P = .001) with no significant difference in waiting list mortality (P = .267) or delisting (P = .915).

Lammers AE, et al. (2021). Ventricular assist devices in paediatric cardiomyopathy and congenital heart disease: An analysis of the German National Register for Congenital Heart Defects. *Int J Cardiol*, 343:37-44. Retrieved from: https://doi.org/10.1016/j.ijcard.2021.08.047

- A multicenter retrospective cohort study performed in Germany from 3/1999 to 11/2015. The aim of the study was to evaluate outcomes in patients who received a VAD due to cardiomyopathy or CHD. Patients with CM were more likely to receive a transplant after VAD support compared to those with CHD (79.5% vs. 28.0%, p < 0.0001). Mortality was higher in the CHD group than the CM group (48% vs. 17.9%;p < 0.0001). There was no significant difference in mortality after transplant between the CM and CHD groups (p = 0.24). Independent predictors of mortality in CHD patients included a diagnosis of CHD (hazard ratio [HR] 4.04, p = 0.001), age at VAD implantation (HR 1.09/year, p = 0.04) and the need for pre-VAD extracorporeal membrane oxygenation (ECMO) support (HR 3.23, p = 0.03).

O'Connor MJ, et al. (2021). Center Variation in Indication and Short-Term Outcomes after Pediatric Heart Transplantation: Analysis of a Merged United Network for Organ Sharing – Pediatric Health Information System Cohort. *Pediatr Cardiol*. Retrieved from: https://doi.org/10.1007/s00246-021-02768-x

- A multicenter retrospective cohort study derived from UNOS and PHIS databases from 1/2004 to 3/2015. The purpose of the study was to evaluate post-transplant outcomes. Thirty-day mortality after transplant in CHD, myocarditis, and CM were 5.5%, 2.9%, and 1.1%, respectively (p < 0.0001). Hospital length of stay differed between the CHD, myocarditis, and CM groups (25 days, 20 days, and 16 days, p < 0.0001). Comprehensive hospital length of stay including readmissions within a year from transplant, were also significantly different between the CHD, myocarditis, and CM groups (34 days, 28 days, and 22 days, respectively; p < 0.0001).

Rochelson E, et al. (2021). Sotalol versus amiodarone for postoperative junctional tachycardia following congenital heart surgery. *Heart Rhythm*, S1547-5271(21)02354-7. Retrieved from: https://doi.org/10.1016/j.hrthm.2021.11.021

- A single retrospective cohort study (n=32) performed in the United States from 12/2015 to 12/2020. The aim of this study was to determine the safety and efficacy of IV sotalol vs. IV amiodarone for postoperative junctional ectopic tachycardia (JET). Amiodarone was successful in treating JET in 75% of cases; sotalol was successful in 83%. The JET rate decreased faster over the first 90 minutes after a sotalol bolus (25 beats/min per hour) than after an amiodarone bolus (8 beats/min per hour) (P < .01); no heart rate difference was seen after 24 hours. Amiodarone infusion was discontinued early because of hypotension/bradycardia in 2 patients; this was not required in any patients receiving sotalol.

Shah MJ, et al. (2021). 2021 PACES Expert Consensus Statement on the Indications and Management of Cardiovascular Implantable Electronic Devices in Pediatric Patients: Developed in Collaboration With and Endorsed by the Heart Rhythm Society (HRS), the American College of Cardiology (ACC), the American Heart Association (AHA), and the Association for European Paediatric and Congenital Cardiology (AEPC) Endorsed by the Asia Pacific Heart Rhythm Society (APHRS), the Indian Heart Rhythm Society (IHRS), and the Latin American Heart Rhythm Society (LAHRS). *JACC Clin Electrophysiol*, 7(11):1437-1472. Retrieved from: https://doi.org/10.1016/j.jacep.2021.07.009

- This document provides guidelines for cardiovascular implantable electronic device use, management, and follow up in pediatric patients.

Das BB, et al. (2021). Contemporary outcomes of durable ventricular assist devices in adults with congenital heart disease as a bridge to heart transplantation. *Artif Organs*. Retrieved from: https://doi.org/10.1111/aor.14092

- A multicenter retrospective cohort study derived from the UNOS thoracic transplantation database from 1/2010 to 12/2019. The aim of this study was to compare the clinical

characteristics, risk factors, and overall survival outcomes in adults with congenital heart disease (ACHD) bridged to transplantation with a ventricular assist device (VAD) versus no-VAD. Waitlist mortality was 38% in the VAD group vs. 17% in the non-VAD group ($p < 0.01$). One year mortality between the groups was not significantly different (15% in VAD group vs .17% in no-VAD group, $p = 0.66$). The study findings suggest that a VAD should be considered an option to support ACHD patients as a bridge to heart transplantation.

Heid CA, et al. (2021). Cardiac transplantation in adults with congenital heart disease: A single center case series. *Clin Transplant*, 35(10):e14430. Retrieved from: https://doi.org/10.1111/ctr.14430

- A single center retrospective case series performed in the United States from 1/2013 to 7/2020. The purpose of this study was to determine the outcomes of patients with CHD who underwent a transplant. Operative times and cardiopulmonary bypass times were longer in the CHD group compared to the non-CHD group (7.5 hours vs. 5.6 hours, $p < 0.001$; 197 minutes vs. 130 minutes, $p < 0.001$). Outcomes (including ejection fraction, ICU readmission, length of ICU stay, adverse cardiac events, and length of hospital stay) were all non-significant between the CHD and non-CHD groups.

Khan A, et al. (2021). Improved heart transplant survival for children with congenital heart disease and heterotaxy syndrome in the current era: An analysis from the pediatric heart transplant society. *J Heart Lung Transplant*, 40(10):1153-1163. Retrieved from: https://doi.org/10.1016/j.healun.2021.07.008

- A multicenter retrospective cohort study derived from the Pediatric Heart Transplant Society (PHTS) database from 1/1993 to 12/2018. The purpose of this study was to evaluate outcomes after transplant in patients with congenital heart disease with heterotaxy syndrome (CHD-HS) compared to other types of CHD. There were no significant differences in waitlist outcomes of transplant, death, or removal due to deterioration between the CHD-HS group and the other CHD group ($p = 0.7$, $p = 0.8$, $p = 0.3$, respectively). One year survival was 77.2% in the CHD-HS group compared to 85.1% in the CHD group ($p < 0.01$). Five-year survival was 66.4% in the CHD-HS group and 75.4% in the CHD group ($p < 0.01$).
- Single ventricle heart disease was an early mortality risk factor for patients with CHD. CHD-HS patients had a lower freedom from infection and from severe rejection, but no difference in vasculopathy or malignancy.

Krishnan GS, et al. (2021). Heart transplantation for patients with single ventricle physiology. *Indian J Thorac Cardiovasc Surg*, 37(6):647-661. Retrieved from: https://doi.org/10.1007/s12055-021-01241-x

- A single center retrospective observational study performed in India from 10/2012 to 10/2019. The purpose of this study was to determine if post-transplant outcomes differed in patients with a single ventricle. Early mortality was 25%, one-year survival was 75%, and five-year survival was 63%. Survival and length of hospital stay were not significantly different between patients with single ventricle physiology compared to those with normal ventricle physiology.

Lu Y, et al. (2021). Favorable outcomes after heart transplantation in Barth syndrome. *J Heart Lung Transplant*, 40(10):1191-1198. Retrieved from: https://doi.org/10.1016/j.healun.2021.06.017

- Barth syndrome (BTHS) is an X-linked disorder that causes cardioskeletal myopathy and neutropenia. A multicenter retrospective cohort study was performed with patients obtained from the Pediatric Health Information Systems (PHIS)-Scientific Registry of Transplant Recipient (SRTR) dataset from North America, the United Kingdom, and Brazil from 2002 to 2016. The aim of this study was to determine post-transplant outcomes in patients with BTHS who have received a heart transplant. There were no significant differences in post-transplant survival between the BTHS and non-BTHS groups ($p = 0.92$). There were no significant differences in the two groups with regards to freedom from PTLD/malignancy ($p = 0.18$) and CAV ($p = 0.41$). Patients in the BTHS group had greater freedom from acute rejection compared to non-BTHS group ($p = 0.02$). The BTHS group also had fewer acute rejection episodes in the first year compared to the non-BTHS group ($p = 0.02$).

Butto A, et al. (2021). Relationship of ventricular assist device support duration with pediatric heart transplant outcomes. *J Heart Lung Transplant*, S1053-2498(21)02521-3. Retrieved from: https://doi.org/10.1016/j.healun.2021.09.011

- A multicenter retrospective cohort study derived from the Pediatric Heart Transplant Study (PHTS) database before 2000. The aim of this study was to determine if patients with less than 30 days of VAD support had different outcomes compared to patients with ≥ 30 days of VAD support. One-year survival was significantly different between the groups at 89.8% survival in the <30 day group and 93.9% in the ≥30 day group ($p = 0.016$). Children with CHD had worse survival compared to children with CM or myocarditis. There were no significant differences in rejection or infections between the two VAD groups.

Scott M and Neal AE. (2021). Congenital heart disease. *Prim Care*, 48(3):351-366. Retrieved from: https://doi.org/10.1016/j.pop.2021.04.005

- A review article that discusses etiology of congenital heart diseases (CHDs), diagnosis of CHDs, and care for CHDs, including care into adulthood.

Kearney K, et al. (2021). Waitlist and post-transplant outcomes for Eisenmenger syndrome: A comparison of transplant strategies. *J Heart Lung Transplant*, 40(8):841-849. Retrieved from: https://doi.org/10.1016/j.healun.2021.04.005

- A multicenter retrospective cohort study derived from the ISHLT registry from 10/1987 to 3/2018. The purpose of this study was to determine outcomes on the transplant waitlist for patients with Eisenmenger syndrome due to atrial septal defect (ES-ASD) vs. patients with ES due to ventricular septal defect (ES-VSD). The study also aimed to compare long-term outcomes in patients with ES treated with a lung transplant with cardiac repair vs. a heart/lung transplant (HLTxp). In the early period of the study (1983 to 2004), ES-ASD patients who received a HLTxp had better survival compared to those who received a lung transplant (LTxp) with cardiac repair ($p = 0.026$). In the late period of the study (2005-2018), ES-ASD patients who received a LTxp with cardiac repair had better survival compared to those with HLTxp ($p= 0.016$).
- In the early period, ES-VSD patients who received a HLTxp had better survival compared to those with LTxp with cardiac repair ($p = 0.016$). In the late period, ES-VSD patients had no significant difference in survival between the two groups ($p = 0.214$).

Dolgner SJ, et al. (2021). Long-term adult congenital heart disease survival after heart transplantation: A restricted mean survival time analysis. *J Heart Lung Transplant*, 40(7):698-706. Retrieved from: https://doi.org/10.1016/j.healun.2021.02.019

- A multicenter retrospective cohort study derived from the UNOS database from 1/2000 to 12/2019. The purpose of this study was to evaluate if patients with ACHD had different outcomes after transplant compared to non-ACHD patients. In the matched cohorts, the ACHD group had an 18-year graft survival of 41.4% vs. 38.2% in the non-ACHD group ($p = 0.02$). Average graft survival times were 11.14 years in the ACHD cohort and 11.40 years in the non-ACHD cohort ($p = 0.38$). Patients in the ACHD group had a higher risk for early mortality ($p < 0.001$).

Huntley GD, et al. (2021). Donor Characteristics and Recipient Outcomes After Heart Transplantation in Adult Congenital Heart Disease. *J Am Heart Assoc*, 10(14):e020248. Retrieved from: https://doi.org/10.1161/jaha.120.020248

- A multicenter retrospective cohort study derived from the Scientific Registry of Transplant Recipients (SRTR) from 2000 to 2016. The aim of this study was to determine if outcomes after transplant are impacted by donor characteristics or waitlist times in patients with ACHD. Thirty-day survival was worse for patients with ACHD vs. non-CHD ($p < 0.001$), but 4-year survival was similar between the groups ($p = 0.31$). Greater than 4-year survival was better in the ACHD group compared to the non-CHD group ($p < 0.001$).
- There were no donor factors associated with early or intermediate mortality in patients with ACHD. However, the study showed that pre-recovery steroid use, meeting high-risk donor criteria, and heart rate were all associated with increased late mortality ($p = 0.006$). The diagnosis of ACHD was associated with a waitlist time of 69.5 days longer than patients with non-ACHD.

Diamant MJ, et al. (2021). No survival benefit associated with waiting for non-lung donor heart transplants for adult recipients with congenital heart disease. *Clin Transplant*, 35(5):e14266. Retrieved from: https://doi.org/10.1111/ctr.14266

- A multicenter retrospective cohort study derived from the UNOS registry from 1/1987 to 12/2016. The purpose of this study was to evaluate post-transplant outcomes in adult patients with CHD who received a non-lung donor (NLD) compared to those with concomitant lung donors. There was no significant difference in waitlist times between recipients of NLD vs. concomitant lung donors (254 days vs. 278 days, $p = 0.31$). There was no significant difference in 1-year mortality between the groups ($p = 0.08$).

Riggs KW, et al. (2021). Transplantation for Congenital Heart Disease: Focus on the Impact of Functionally Univentricular versus Biventricular Circulation. *World J Pediatr Congenit Heart Surg*, 12(3):352-359. Retrieved from: https://doi.org/10.1177/2150135121990650

- A multicenter retrospective cohort study derived from the UNOS and PHIS databases from 2006 to 2017. The aim of this study was to determine if single ventricle patients with CHD had different outcomes compared to biventricular patients with CHD. Single ventricle patients had higher sensitization (36.0% vs 26.7%, $p = 0.010$). However, single ventricle patients were less likely to need ECMO or VAD support at transplant (ECMO use 5.0% vs. 10.3%, $p < 0.001$; VAD use 4.7% vs. 11.5%, $p < 0.001$). There was no significant difference in survival between the two groups ($p = 0.893$).

Kainuma A, et al. (2021). Cardiac transplantation in adult congenital heart disease with prior sternotomy. *Clin Transplant*, 35(4):e14229. Retrieved from: https://doi.org/10.1111/ctr.14229

- A single center retrospective cohort study performed in the United States from January 2008 to December 2018. The purpose of this study was to determine early and long-term outcomes in ACHD patients with a prior sternotomy. There was no significantly different 10-year survival between patients with ACHD and patients without ACHD ($p = 0.429$). There was no significant difference in 10-year survival between the single ventricle and biventricular groups ($p = 0.467$).

de Miguel IM and Ávila P. (2021). Atrial Fibrillation in Congenital Heart Disease. *Eur Cardiol*, 16:e06. Retrieved from: https://doi.org/10.15420/ecr.2020.41

- A review article discussing the epidemiology, pathophysiology, clinical impact, and management of atrial fibrillation in adults with congenital heart disease.

Baumgartner H, et al. (2021). 2020 ESC Guidelines for the management of adult congenital heart disease. *Eur Heart J*, 42(6):563-645. Retrieved from: https://doi.org/10.1093/eurheartj/ehaa554

- An update of the guidelines for adult congenital heart disease between 2010 to 2020.

Kinsella A, et al. (2020). Post-transplant survival in adult congenital heart disease patients as compared to dilated and ischemic cardiomyopathy patients; an analysis of the thoracic ISHLT registry. *Clinical Transplantation*, 34(9). Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32478908/

- Adult heart transplant patients were analyzed from the ISHLT registry to evaluate survival outcomes of adult congenital heart disease (ACHD) specifically compared to ischemic (ICM) and dilated cardiomyopathy (DCM). In the 30,130 patients included, the one-year survival was 78.3% in ACHD, 84.3% in ICM, and 86.2% in DCM patients and they found that ACHD and ICM patients were at significantly higher mortality risk than DCM. Graft failure-related mortality was higher in the ACHD group within the first year of post-transplant as compared to DCM group, while there was no difference between groups in post year 1.

Freisinger E, et al. (2020). Current use and safety of novel oral anticoagulants in adults with congenital heart disease: results of a nationwide analysis including more than 44,000 patients. *Eur Heart J*, 41(43):4168-4177. Retrieved from: https://doi.org/10.1093/eurheartj/ehaa844

- A multicenter retrospective cohort study derived from the BARMER database in Germany from 2005 to 2018. The aim of this study was to determine long-term safety and efficacy of NOACs vs. VKAs in ACHD patients. Within 1 year of new anticoagulation, 9.5% of ACHD patients required hospitalization for bleeding and 15.5% required hospitalization within the first 2 years of

anticoagulation. Bleeding rates in the first year were higher in patients on NOACs (11.5%) vs. VKAs (8.8%) (p = 0.001). There was no difference between the groups after the first year of anticoagulation. Major thromboembolic events occurred more frequently in ACHD patients on NOACs (3.7%) vs. VKAs (2.8%) in the first year and in the second year (6.4% vs. 4.7%) (p <0.05 in both years).
- There were also a higher number of major adverse cardiovascular events in ACHD patients on NOACs compared to VKAs (p < 0.05). All-cause mortality was higher in the NOAC group compared to the VKA group at both 1 year (4.0% vs. 2.8%) and 2 years (6.8% vs. 5.0%) (p < 0.05).

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.

5.7.3 Valvular Heart Disease

Kuno T, et al. (2021). Duration of Antiplatelet Therapy Following Transcatheter Aortic Valve Replacement: Systematic Review and Network Meta-Analysis. Am J Heart Assoc. 4(10):e019490. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33870703/
- Meta-analysis investigating outcomes between single antiplatetet therapy v. 3- or 6-month DAPT use following TAVR. Rates of major or life-threatening bleeding were significantly higher in the 3- and 6-month DAPT groups (RR 2.23, 95% CI 1.33-3.40, p=0.016; RR 2.54, 95% CI 1.49-4.33, p=0.007) compared to the single antiplatelet therapy group. There was no difference in rates of stroke and all-cause mortality between the three groups.

Melgaard L, et al. (2021). Effectiveness and Safety of NOAC Versus Warfarin in Patients With Atrial Fibrillation and Aortic Stenosis. *J Am Heart Assoc*, 10(23):e022628. Retrieved from: https://doi.org/10.1161/jaha.121.022628
- A multicenter retrospective cohort study derived from 4 different Danish nationwide registries from 2013 to 2018. The purpose of this study was to determine thromboembolic and bleeding outcomes in patients on NOACs vs. warfarin due to atrial fibrillation (AF) with aortic stenosis. Three year thromboembolic-free survival was similar between the NOAC and warfarin groups (94.0% vs. 96.0%). Three year survival free from major bleeds was 87.6% in the NOAC group and 83.6% in the warfarin group.

Izumi C, et al. (2021). Antithrombotic Therapy for Patients With Atrial Fibrillation and Bioprosthetic Valves – Real-World Data From the Multicenter, Prospective, Observational BPV-AF Registry. *Circ J*. Retrieved from: https://doi.org/10.1253/circj.cj-21-0564
- A multicenter, prospective, observational study derived from the BPV-AF registry from September 2018 to October 2019. The aim of this study was to evaluate efficacy and safety of DOACs, warfarin, and antiplatelets in patients with atrial fibrillation (AF) and bioprosthetic valves (BPV). The event rate for stroke or systemic embolism was 2.10%/year (95% CI, 1.22–3.61) in warfarin-

treated patients and 1.48%/year (95% CI, 0.62–3.55) in DOAC-treated patients. The event rate for major bleeding was 1.77%/year (95% CI, 0.98–3.20) in warfarin-treated patients and 2.08%/year (95% CI, 0.99–4.36) in DOAC-treated patients. There were no significant differences in stroke or systemic embolism or major bleeding event rates between warfarin- and DOAC-treated patients (log-rank P=0.500 and P=0.746, respectively).

Vahanian A, et al. (2021). 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*, 00:1-72. Retrieved from: https://doi.org/10.1093/eurheartj/ehab395

- An update to the previous 2017 guidelines which includes patient evaluation, risk stratification, and management.

Huda SA, et al. (2021). Management of Life-Threatening Bleeding in Patients With Mechanical Heart Valves. *Cureus*, 13(6):e15619. Retrieved from: https://doi.org/10.7759/cureus.15619

- A review article discussing the management of major bleeding events in patients with mechanical heart valves.

Kobari Y, et al. (2021). Aspirin Versus Clopidogrel as Single Antithrombotic Therapy After Transcatheter Aortic Valve Replacement: Insight From the OCEAN-TAVI Registry. *Circ Cardiovasc Interv*, 14(5):e010097. Retrieved from: https://doi.org/10.1161/circinterventions.120.010097

- A multicenter retrospective cohort study derived from the OCEAN-TAVI registry in Japan from 10/2013 to 5/2017. The purpose of this study was to evaluate the outcomes of aspirin vs. clopidogrel after transcatheter aortic valve replacement. All-cause deaths were not statistically different between the groups in patients with (aspirin, 17.5%; clopidogrel, 11.1%; log-rank P=0.07) and without (aspirin, 29.6%; clopidogrel, 20.1%; log-rank P=0.15) anticoagulation at 2 years after TAVR, whereas clopidogrel was associated with a lower cardiovascular mortality at 2 years in patients with (aspirin, 8.5%; clopidogrel, 2.7%; log-rank P=0.03) and without (aspirin, 18.0%; clopidogrel, 5.2%; log-rank P=0.02) anticoagulation. There were no significant differences in 2-year incidence of major bleeding or stroke between the groups. The all-cause death rate at 2 years was higher in the warfarin group than in the DOAC group in patients on aspirin (warfarin, 28.0%; DOAC, 5.5%; P=0.002), while it was not different in patients on clopidogrel (warfarin, 9.8%; DOAC, 12.8%; P=0.70).

Otto CM, et al. (2021). 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive summary: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*, 143(5):e35-e71. Retrieved from: https://doi.org/10.1161/cir.0000000000000932

- An updated guideline providing recommendations for the diagnosis and management of 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

Yaranov DM, et al (2024). Anticoagulation Bridging in Patients With Left Ventricular Assist Device: A Regional Analysis of HeartMate 3 Recipients. *ASAIO J*. 2024;70(2):93-98. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37862687/

- Analysis of the MOMENTUM-3 trial focusing on outcomes in HM3 patients with subtherapeutic INR (<2) who were bridged (N=56) vs not bridged (N=179) with subcutaneous or IV anticoagulants. There was no difference in individual outcomes or composite of death, rehospitalization, CVA, or bleeding events between bridging and non-bridging.

Chesdachai S, et al (2023). Clinical Characteristics and Outcomes of Clostridioides difficile Infection in Patients With Left Ventricular Assist Device. ASAIO J. 69(10):950-955. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37367716/

- Retrospective matched cohort study between 2010-2022 determining risk factors and outcomes in LVAD patients who developed Clostridioides difficile infection (CDI, N=47) vs those who did not. Median time from LVAD implantation to CDI was 147 days. Oral vancomycin was used in 55.3% of patients. 27.7% required treatment extension and 6.4% developed recurrent CDI. CDI was associated with antibiotic exposure with 90 days and higher 1-year mortality than matched controls.

Mansoor AE,et al (2023). Experience with dalbavancin for long-term antimicrobial suppression of left ventricular assist device infections. *Transpl Infect Dis*. 25(4):e14068. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37159539/

- Retrospective, single-center review of patients with LVAD-related infections between 1/2011 to 11/2022 whose management included dalbavancin (N=10). Corynebacterium striatum was the most common causative organism (6/10). 3 patients had deep driveline infections, 4 had recurrent superficial driveline infections, and 3 had pocket infections. Mean time from initial infection to dalbavancin start was 77 weeks, and 9 patients continued therapy for >90 days. Breakthrough infections were seen in 2 patients. No treatment-related adverse events were noted.

Inglis SS, et al (2023). Infections in Patients With Left Ventricular Assist Devices: Current State and Future Perspectives. ASAIO J. 69(7):633-641. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37145863/

- Review article discussing VAD-specific and VAD-related infections: epidemiology, risk factors, microbiology, diagnosis, prevention, medical management, surgical management, transplant considerations, and future perspectives.

Mehra M. (2023). Aspirin and Hemocompatibility Events With a Left Ventricular Assist Device in Advanced Heart Failure: The ARIES-HM3 Randomized Clinical Trial. *JAMA*. 330(22):2171-2181. Retrieved from: https://jamanetwork.com/journals/jama/fullarticle/2811936?resultClick=1

- International, randomized, double-blind, placebo-controlled study of 589 patients with the HM3 LVAD randomized to aspirin 100 mg/day or placebo, both with vitamin K antagonists, that sought to determine if exclusion of aspirin is safe and decreases bleeding. Placebo was noninferior to aspirin therapy for the composite end point of survival free of stroke, pump thrombosis, major bleeding, or arterial peripheral thromboembolism at 12 months (68.1% aspirin vs 74.2 % placebo, p<0.001). This was driven by reduced bleeding events in the placebo group (22.5% vs 28.2%).

Carey MR, et al. (2023). Aortic Root Thrombosis in patients with HeartMate 3 left ventricular assist device support. *J Heart Lung Transplant*. S1053-2498(23)02007-7. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37739242/

- Single center retrospective analysis of patients that underwent HM3 implantation (n=197) to evaluate the incidence and timing of aortic root thrombosis (ART) and its impact on clinical outcomes. Nineteen (9.6%) patients developed ART and 15 (7.6%) had at least moderate aortic insufficiency. Development of ART was associated with an increased risk of death, stroke or aortic valve intervention (subhazard ratio 3.60 CI 1.71-7.56) but not with an increased risk of death or stroke (SHR 2.12 CI 0.86-5.22).

Alba A, et al. (2023). The impact of obesity and LVAD-bridging on heart transplant candidate outcomes: a linked STS INTERMACS – OPTN/UNOS data analysis. *J Heart Lung Transplant*. 42(11):1587-1596. Retrieved from: https://www.jhltonline.org/article/S1053-2498(23)01893-4/fulltext

- Retrospective analysis of linked patients from the INTERMACS and OPTN/UNOS databases to evaluate the impact of BMI on mortality in patients with (n=11,216) and without (n=17,122) an LVAD. BMI was categorized as underweight (<18.5 kg/m2), normal weight (18.5–24.99 kg/m2), overweight (25–29.99 kg/m2), and obese (≥30 kg/m2).
- Bridged candidates were more frequently obese (37.3% vs 28.6%, p < 0.001). An increased waitlist mortality was seen in LVAD-bridged patients that were overweight (HR 1.18 CI 1.02-1.36) or obese (HR 1.35 CI 1.17-1.56) and no difference was seen in normal weight candidates (HR 1.02 CI 0.88-1.19). Post-transplant there was not a significant difference in mortality in bridged vs nonbridged patients regardless of BMI (p <0.001).

George AN, et al. (2022) Complications in children with ventricular assist devices: systemic review and meta-analyses. *Heart Fail Rev*. 27(3): 903-913. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33661404/

- Systematic review and meta-analysis compiling studies reporting risk factors and etiologies of complications of VAD support in children including thrombosis, neurological problems, infections, bleeding and mortality.

Jain R, et al. (2022). De novo human leukocyte antigen allosensitization in Heartmate 3 versus Heartmate II left ventricular assist device recipients. *ASAIO Journal*. 2022;68(2):226-232. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33883507/

- Retrospective chart review investigated the differential effect of HM3 (n=38) implantation on HLA allosensitization in comparison to HMII (n=34). Development of high-level (MFI >10,000) antibodies was significantly lower in HM3 than HMII patients (5.3% vs 20.6%, p=0.049). Fewer HM3 patients had a positive PRA than HMII patients (39.4% vs 70.0%, p=0.015). Among transplanted patients, those who had developed *de novo* sensitization on LVAD support showed a trend toward incidence of moderate to severe grade rejection compared with unsensitized patients (23.8% vs 4.8%, p=0.078).

Srinivasan AJ, et al. (2022). Recent changes in durable left ventricular assist device bridging to heart transplantation. *ASAIO Journal*. 2022;68(2):197-204. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33788800/

- Retrospective analysis using the UNOS database evaluated the impact of the recent UNOS allocation policy change on outcomes of patients bridged with durable left ventricular assist devices (LVADs) to orthotopic heart transplantation (OHT). OHT following durable LVAD bridging decreased from 45% to 34% (p < 0.001). Patients in the new-policy cohort were at higher risk due to more extracorporeal membrane oxygenation bridging, more mechanical right ventricular support, greater pretransplant ICU admission, more need for total functional assistance, older donor age, and longer ischemic times. However, early post-OHT survival was comparable at 30 days, 90 days, and 6 months.

Lambadaris M, et al. (2022). Association between continuous-flow left ventricular assist device infections requiring long-term antibiotic use and post-heart transplant morbidity and mortality. *J Card Surg*, 37(1):96-104. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34651943/

- Single-center retrospective observational cohort study. Among 75 LVAD patients, 21% had chronic LVAD-related infection on suppressive antibiotics, 40% had resolved infection, and 39% had no infections. LVAD patients with infections did not have a significantly higher risk of infection (OR 1.6 CI 0.5-6.5), rejection (OR 1.0 CI 0.1-11.7), or mortality (OR 3.1 CI 0.6-18.7) compared to those without chronic infections at any time point after transplant.

Immohr MB, et al. (2022). Impact of pre-transplant left ventricular assist device support duration on outcome after heart transplantation. *Interact Cardiovasc Thorac Surg*, 2022;34(3):462-469. Retrieved from: https://doi.org/10.1093/icvts/ivab265

- A single center, prospective study aiming to determine if LVAD implantation impacts subsequent heart transplant outcomes. Study participants were separated into groups based on how long they required LVAD support before transplant (Group 1: <90 days, n=14; Group 2: 90 days to 1 year, n=31; Group 3: 1 to 2 years, n=29; Group 4: >2 years, n=24). The study showed no difference in graft ischemia time, post-operative hospital length of stay, or ICU length of stay. The study did show that time requiring mechanical ventilation differed between groups (group 2 = 49 hours, group 3 = 103 hours). Groups 2 and 3 had significantly different incidences of severe primary graft dysfunction that required VA-ECMO (25.8% vs. 41.4%). There were no statistically different rates of acute graft rejection based LVAD support duration (Group 1 = 28.6%, Group 2 = 3.3%, Group 3 = 7.1%, Group 4 = 12.5%; P=0.06). Duration of LVAD support did not have an impact on 30-day survival (p = 0.48) or on 1-year survival (p = 0.74).

DeFilippis EM, et al. (2021). ECMO as a Bridge to Left Ventricular Assist Device or Heart Transplantation. *JACC Heart Fail*, 9(4):281-289. Retrieved from: https://doi.org/10.1016/j.jchf.2020.12.012

- A multicenter retrospective cohort study to compare outcomes between patients receiving ECMO as a bridge to LVAD (n=587) compared to as a bridge to heart transplant (HT) (n=319). Patients bridged to LVAD had a longer hospital length of stay compared to those bridged to transplant (p = 0.004). Patients bridged to LVAD were more likely to be on IV inotrope therapy (p < 0.001). Competing risk analysis showed no significant difference in morality when bridged to LVAD or bridged to transplant (p = 0.478). Of the patients bridged to transplant, mortality was 29.3% at 1 year, 33.4% at 2 years, and 38.2% at 5 years. Of the patients bridged to LVAD, mortality was 30.8% at 1 year, 37.4% at 2 years, and 43.5% at 5 years.

King PM, et al. (2020). Right heart failure while on left ventricular assist device support is associated with primary graft dysfunction. *ASAIO J*, 66(10):1137-1141. Retrieved from: https://doi.org/10.1097/mat.0000000000001156

- A single center retrospective cohort aimed to determine the post-transplant outcomes in patients with right heart failure (RHF) requiring LVAD support (n=41) compared to those without RHF requiring LVAD support (n=100). Primary graft dysfunction (PGD) occurred more in the RHF group compared to the group without RHF (43.9% vs 14.0%, p<0.001). Thirty-day mortality (19.5% vs. 1.0%, p<0.001) and 1-year mortality (22.0% vs. 6.0%, p=0.013) were significantly higher in the RHF group.

Lescroart M, et al. (2020). Pulsatility in ventricular assistance devices: A translational review focused on applied haemodynamics. *Arch Cardiovasc Dis*, 113(6-7):461-472. Retrieved from: https://doi.org/10.1016/j.acvd.2020.03.017

- A review article discussing pulsatility and LVADs to understand physiopathology and adverse effects of continuous-flow devices.

Miller RJH, et al. (2020). Transplant outcomes in destination therapy left ventricular assist device patients. *ASAIO*. 66(4):394-8. Retrieved at: https://www.ncbi.nlm.nih.gov/pubmed/31192848

- Single center cohort study comparing outcomes of patients that underwent transplantation after receiving an LVAD with the intent of use as bridge to transplant (BTT) (n=57) vs bridge to destination (DT) (n=35). There was no significant difference in 1-year survival between heart transplant recipients who had LVADs implanted as BTT versus DT prior to transplantation (HR 0.89 CI 0.33-2.41, p=0.82). 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*. 66(3):261-7. Retrieved at: https://www.ncbi.nlm.nih.gov/pubmed/32101996

- Query of the UNOS database to determine the types of induction therapy (IT) used in patients with LVADs and determine the clinical outcomes. There was no significant difference in the primary outcomes of graft survival (p=0.173), freedom from hospitalization for rejection (p=0.211), and freedom from hospitalization for infection (p=0.300) between BTT LVAD patients who received IT (n=3,978) and those who did not (n=4,129). LVAD patients who received IT had

increased freedom from transplant coronary artery disease (TCAD) (p=0.004), with increased freedom from TCAD among those who received antithymocyte globulin compared to basiliximab (p=0.004).

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*. 35(1):34-9. Retrieved at: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/26296960/

- Retrospective analysis of patients in the ISHLT registry bridge to transplant with LVADs (n=2,152) were assessed for risk factors for mortality within 30 days of transplant. Post-transplant survival at 30 days was 95.5%. Risk factors associated with mortality at 30 days were ventilator support at transplant (HR 5.00 CI 1.51-16.58), female recipient/male donor (HR 3.29 CI 1.90-5.72), history of hemodialysis (HR 2.51, CI 1.14-5.51) and history of coronary bypass grafting (HR 1.89 CI 1.19-3.00). Other factors associated with increased mortality were increasing recipient age, BMI, creatinine, and total bilirubin.

Ko BS, et al. (2016) Immunologic effects of continuous-flow left ventricular assist devices before and after heart transplant. *J Heart Lung Transplant*. 35(8):1024-30. Retrieved at: https://www.ncbi.nlmv.nih.gov/pubmed/27316382

- Retrospective review of patients with LVADs being considered for cardiac transplantation (n=268) were assessed for allosensitization (defined as cPRA >10%). Following continuous flow LVAD implantation, 30 patients became newly allosensitized. Those with new LVAD-associated allosensitization had a higher risk of ACR (p=0.049) and AMR (p=0.018).

Kidambi S, et al. (2015) Clinical outcomes in sensitized heart transplant patients bridged with ventricular assist devices. *Clin Transplant*. 29(6):499-505. Retrieved at: https://pubmed.ncbi.nlm.nih.gov/25773536/

- Retrospective review of patients with LVADs as a bridge to transplant (BTT) (n=38, 17 sensitized and 21 non-sensitized) had cPRA levels measured to measure the impact of allosensitization on outcomes. Sensitization was defined as peak cPRA ≥ 10%. After transplant, there was no difference mean time to high-grade acute cellular rejection (18.3 months vs 36.9 months, log rank p=0.208). Five sensitized patients experienced AMR episodes vs none in the non-sensitized group and all five patients died. There was a higher incidence of infection in the sensitized group (52.9% vs 19.0%, p=0.03).

5.8 Pre-Transplant Considerations

Jain, R., & Kittleson, M. M. (2024). Evolutions in Combined Heart-Kidney Transplant. *Curr Heart Fail Rep*, 21(2), 139–146. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38231443/

- Review article discussing management strategies, outcomes, and allocation policies for simultaneous heart-kidney transplant (SHKT) candidates since the new UNOS organ allocation policy adopted in September 2023, which enforced stricter eligibility criteria for SHKT and safety net kidney transplants

Singal A, et al. (2024). Use and Outcomes of Hepatitis B Virus-Positive Grafts for Kidney or Heart Transplantation in the United States From 1999 to 2021. *Transplantation*. 108(3):693-702. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37953470/

- Retrospective analysis of UNOS data to determine the outcomes of heart transplant recipients with hepatitis B positive grafts. Fifty-one recipients of HBV-positive hearts were analyzed. Survival at 1, 3, 5, and 10 years was similar for recipients of HBV-positive hearts (83.4%, 67.8%, 64.9%, 41.9%) compared to recipients of HBV-negative hearts (88.3%, 80.1%, 72.8%, 38.9%) (log-rank p=0.471). None of the 51 recipients developed HCC.

Kuroda, T., Miyagi, C., Fukamachi, K., & Karimov, J. H. (2023). Biventricular assist devices and total artificial heart: Strategies and outcomes. *Front Cardiovasc Med.* 9:972132. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36684573/

- Review of different pre-transplant mechanical circulatory support options and associated clinical outcomes

DeFilippis E, et al. (2023). Association between calculated panel reactive antibody and waitlist outcomes in the 2018 heart allocation system. *J Heart Lung Transplant*. 42(10):146901477. Retrieved from: https://www.jhltonline.org/article/S1053-2498(23)01874-0/fulltext

- Retrospective analysis of adult waitlist outcomes in OPTN based on cPRA. Of the 13,325 patients listed in the study period, 11,214 (84%) had a cPRA ≤35, 1,260 (9.5%) had a cPRA between 35-90, and 293 (2.2%) had a cPRA ≥ 90 at listing. Candidates with elevated cPRA were less likely to be on inotropes (p = 0.002), supported by an intra-aortic balloon pump at the time of listing (p < 0.001), and had lower pulmonary artery systolic pressures (p < 0.001). Higher cPRA was associated with decreased heart transplant (aHR 0.39 CI 0.33-0.47 vs low cPRA).

Ahmed H, et al. (2023) Donation after circulatory death significantly reduces waitlist times while not changing post-heart transplant outcomes: A United Network for Organ Sharing Analysis. *J Heart Lung Transplant*. S1053-2498(23)02076-4. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37863451/

- Retrospective analysis of UNOS data to determine posttransplant outcomes and waitlist times for recipients of DCD hearts (n=425) vs DBD hearts (n=9,977). Recipients of a DCD organ were more likely to be White (67% vs 60%, p=0.002), on LVAD support (40% vs 32%, p<0.001) and listed as status 4-6 (60% vs 24%, p<0.001). Survival rates between DCD and DBD recipients were similar at 6 months, 12 months, and 24 months (DCD: 94%, 92%, 80% and DBD: 92%, 90%, 86%; p=0.72). Adjusted waitlist time was shorter in the DCD group (21 vs 31 days, p<0.001).

Nunez M, Kelkar AA. (2023). Hepatitis C and heart transplantation: An update. *Clin Transplant*. 37(10):e15111. Retrieved from: https://onlinelibrary.wiley.com/doi/10.1111/ctr.15111

- Review article discussing outcomes after transplantation and treatment options after transplantation.

Vaidya G, et a. (2023). Patterns and outcomes of COVID-19 donor utilization for heart transplant. *Clin Transplant*. 37(4):e14917. Retrieved from: https://onlinelibrary.wiley.com/doi/10.1111/ctr.14917

- Retrospective analysis of the UNOS database of heart transplant recipients of COVID-19 positive donors to describe post-transplant outcomes. Of the 7,698 donors with antigen or NAT tests available, 177 (2.3%) were positive. There was no difference in length of stay (median 16 vs 17 days, p=0.9) or acute rejection episodes prior to discharge (3% vs 8%, p=0.1). Ninety day mortality was similar in both groups (5% for both, p=0.9).

Jimenez DC, et al. (2022). Cardiac transplantation after heparin-induced thrombocytopenia: A systematic review. *Clinical Transplantation*. 36(2):e14567. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34927287/

- Systematic review included 33 patients from 21 studies who had clinical diagnosis of Heparin induced thrombocytopenia (HIT) and required heart transplantation (HTx). Intraoperatively, 20 (61%) patients were given unfractionated heparin (UFH), while 21 (39%) were given alternative anticoagulants. The alternative agent subgroup required more antifibrinolytics (54% vs 10%, p = 0.02) and clotting factors (69.2% vs 15.0%, p < 0.01). Perioperative thrombosis occurred more in the alternative agent subgroup (53.8% vs 0%, p < 0.01). More patients in the alternate agent subgroup required post-operative transfusions (54% vs 0%, p < 0.01). Thirty-day mortality was comparable between the subgroups (15.4% vs 15.0%, p=1.00).

O'Connell G, et al. (2022). Impact of UNOS allocation policy changes on utilization and outcomes of patients bridged to heart transplant with intra-aortic balloon pump. *Clinical Transplantation*. 36(2):e14533. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34786769/

- Retrospective UNOS database review of heart transplant candidates with intra-aortic balloon pumps (IABPs) listed or transplanted before (n=419) and after (n=1637) the UNOS policy changes. Patients with IABPs listed after the policy change were more likely to receive a

transplant and were transplanted more quickly with a 90% probability of receiving a transplant by 90 days vs 65% pre policy change ($p < 0.001$). One-year post-transplant survival was comparable before and after the policy change (HR 1.706 CI 0.896-3.247, p=0.1037).

Finnan MJ, et al. (2022). 30 years of heart transplant: outcomes after mechanical circulatory support from a single center. *Ann Thorac Surg*, 113(1):41-48. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33675715/

- Single-center retrospective review of OHT patients from 1988 to 2019. Primary transplantation rates declined from 88% to 14% over the course of the study as the use of MCS increased. Survival of patients treated with continuous-flow LVAD and temporary MCS was noninferior to that of primary transplantation on Kaplan-Meier survival analysis (p=0.22). There were no major differences in postoperative complications based on pretransplantation MCS status, but those with MCS support trended toward requiring blood transfusions (p=0.06), post-operative IABP use (p=0.06), and longer time to discharge (p=0.06).

Carter KT, et al. (2022). Venoarterial extracorporeal membrane oxygenation is a viable option as a bridge to heart transplant. *J Thorac Cardiovasc Surg*, 163(1):140-147.e4. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32928549/

- Retrospective analysis using UNOS database that analyzed restricted mean survival time of OHT recipients based on MCS requirements. Restricted mean survival time was higher in patients who did not require mechanical support (16.6 months), LVAD (16.5 months), IABP (11.2 month), and biventricular assist device (6.6 months) when compared with recipients who received ECMO. Use of RVAD and TAH resulted in restricted mean survival time that was similar to patients receiving ECMO.

Wayda B, et al. (2021). Optimal patient selection for simultaneous heart-kidney transplant: A modified cost-effectiveness analysis. *Am J Transplant*. Retrieved from: https://doi.org/10.1111/ajt.16888

- Multicenter retrospective cohort study and cost-effectiveness analysis comparing those who received a simultaneous heart-kidney transplant (SHK) to those who received transplants using the Safety Net strategy. Compared to the Safety Net strategy, the SHK strategy resulted in 0.98 more QALYs, 0.37 more kidneys used, and an absolute reduction in 1-year mortality of 8.1% in patients with moderate reversibility (25%) of kidney function and of average age (50-59). Differences in mortality and QALYs gained were more pronounced for those with low reversibility (10%) and less pronounced in those with high reversibility (50%).

Melvinsdottir I, et al. (2020). Heart and kidney transplant: Should they be combined or subsequent? *ESC Heart Fail*, 7(5):2734-2743. Retrieved from: https://doi.org/10.1002/ehf2.12864

- Multicenter retrospective cohort study of UNOS data to determine if outcomes differed between patients who received a heart and kidney transplant (HKTx, n=715) compared to a kidney transplant after heart transplant (KAH, n=130). Patients in the HKTx group had a higher risk for death compared to patients in the KAH group on Kaplan-Meier survival analysis ($p = 0.001$). This was maintained regardless of dialysis status, age, gender, baseline eGFR, or center selection bias. Major causes of death in the HKTx group included bacterial infection, malignancy, cardiac arrest, and multiple organ failure, while with the major causes of death in the KAH group included kidney failure, malignancy, or unknown cause of death.

Giordanino EF, et al. (2020). Short-term mechanical circulatory support devices as bridge to heart transplantation: A prospective single-center experience in Argentina. *Clin Transplant*, 34(7):e13888. Retrieved from: https://doi.org/10.1111/ctr.13888

- Single center prospective cohort study to determine if use of ECMO (n=14) or centrifugal pump (CP, n=23) before transplant as a bridge to therapy impacted outcomes after transplant. While on MCS, the most common complications were AKI (54.1%), bleeding (35.1%), and vasoplegic syndrome (35.1%). Thirty patients survived to transplant, with 7 patients dying on CP support. After transplant, PGD was seen in 8 patients (6 ECMO, 2 CP) and AKI in 18 patients (7 ECMO, 11 CP). Length of hospital stay after transplant was not different (21 vs 18 days, p=0.84) and 30-day mortality was not significantly different (14.3% vs 31.3%, p=0.4).

5.9 Post-Transplant Considerations

Holzhauser L, et al. (2023). The End of Endomyocardial Biopsy?: A Practical Guide for Noninvasive Heart Transplant Rejection Surveillance. *JACC. Heart failure*, 11(3), 263–276. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36682960/

- Review article providing clinical guidance and evidence for using gene expression profiling and donor-derived cell-free DNA to non-invasively monitoring for rejection

Batra J, et al. (2023). Early post-transplant leukopenia in heart transplant recipients and its impact on outcomes. *Clin Transplant*. 37(5):e14934. Retrieved from: https://onlinelibrary.wiley.com/doi/10.1111/ctr.14934

- Retrospective single-center analysis of 506 heart transplant recipients that aimed to describe incidence of leukopenia and its impact on 1-year outcomes. Leukopenia developed in 184 (36%) patients within 90 days (median 15.5 days for first episode). Early leukopenia was associated with a higher mortality at 1-year (6.6% vs. 2.1%, p = .008; adjusted HR 3.0 CI 1.2-7.2). There was no difference in rates of infection or rejection.

Bart N, et al. (2023) Tricuspid Regurgitation After Heart Transplantation: The Cause or the Result of Graft Dysfunction? *Transplantation*. 107(6):1390-1397. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36872474/

- Retrospective, single-center study of 163 heart transplant recipients that sought to describe the development of tricuspid regurgitation (TR) during the first 2 years post-transplant. Thirty-six (22%) patients developed moderate-severe TR and 5-year survival was similar between the two groups. Those with late progressive moderate-severe TR had a higher 2-year mortality than those with moderate-severe TR immediately after transplant (44% vs 8%, p<0.05).

Shoji S, et al. (2022). Incidence and long-term outcome of heart transplantation patients who develop postoperative renal failure requiring dialysis. *J Heart Lung Transplant*, 41(3):356-364. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34953720/

- Retrospective analysis using the UNOS database to determine outcomes of heart transplant recipients who develop postoperative renal failure requiring dialysis. A total of 28,170 patients were included, of which 3,371 (12%) required dialysis immediately post-heart transplantation. Predictors for acute renal failure included longer ischemic time, serum creatinine at transplantation >1.2 mg/dL, prior cardiac surgery, higher recipient body mass index, support of mechanical ventilation or extracorporeal membrane oxygenation, and history of congenital heart disease or restrictive/hypertrophic cardiomyopathy (p < 0.05). Patients on posttransplant dialysis had a higher risk of all-cause mortality (aHR 5.2 CI 4.7-5.7, p<0.001), 30-day mortality (aHR 7.7 CI 6.3-9.6, p<0.001), and 1-year mortality (aHR 7.5 CI 6.6-8.6, p < 0.001).

Youn JC, et al. (2022). Post-transplantation outcomes of sensitized patients receiving durable mechanical circulatory support. *J Heart Lung Transplant*, 41(3):365-372. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34895990/

- Single-center, prospective, observational study compared the outcomes of sensitized-mechanical circulatory support (MCS) patients with sensitized non–MCS patients, non–sensitized MCS patients, and non–sensitized non–MCS patients. Compared to sensitized patients without MCS, sensitized MCS patients had higher 1-year freedom from AMR at 1-year (76.4% vs 84.2%) and had an earlier decline in panel reactive antibody (PRA) levels. Compared to non–sensitized MCS patients and non–sensitized non–MCS patients, sensitized MCS patients showed comparable rates of primary graft dysfunction (17.9%, 19.4%, 5.3%),1-year survival (91.0%, 88.8%, 89.5%), and 1-year freedom from AMR (98.5%, 89.6%, 84.2%).

Han J, et al. (2022). Impact of using higher-risk donor hearts for candidates with pre-transplant mechanical circulatory support. *J Heart Lung Transplant*. 41(2):237-243. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34815161/

- Retrospective analysis using the UNOS database evaluated post-heart transplant (HTx) outcomes after use of higher-risk donor hearts for candidates supported with pre-HTx mechanical circulatory support (MCS). Patients supported with pre-transplant ECMO or surgical BiVAD (n=374) who received higher-risk donor hearts had 1 year survival comparable to recipients of standard criteria donor hearts (HR 1.14 CI 0.67-1.93, p=0.64). Patients supported with pre-transplant IABP who received higher-risk donor hearts had 1 year survival comparable to recipients of standard criteria donor hearts (HR 0.80 CI 0.52-1.22, p=0.30). Patients supported with pre-transplant durable LVAD who received higher-risk donor hearts had 1 year survival inferior to recipients of standard criteria donor hearts (HR 1.37 CI 1.11-1.70, p=0.004).

Hirji SA, et al. (2022). Contemporary nationwide heart transplantation and left ventricular assist device outcomes in patients with histories of bariatric surgery. *Journal of Cardiac Failure*. 2022;28(2):330-333. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34509598/

- Retrospective analysis assessing the outcomes of patients with a history of bariatric surgery that underwent heart transplant or LVAD implantation compared to those with BMI ≥35. In-hospital mortality in the HT cohort was not different between the two groups (aOR 0.77 CI 0.13-4.40). The incidence of bleeding requiring transfusion, acute kidney injury, vascular complications, and rejection were 19.1%, 76.2%, 76%, and 14.3%, respectively. These risk-adjusted hospital outcomes were not significantly different from those of obese patients without previous bariatric surgery.

Zhou L, et al. (2022). Noninvasive methods to reduce cardiac complications post heart transplant. *Current Opinion in Organ Transplantation*. 2022;27(1):45-51. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34907978/

- The review article summarized newer noninvasive screening techniques for the detection of clinically significant rejection and potential new biomarkers and therapies in preventing allograft vasculopathy.

Vest AR, et al. (2022). New-onset diabetes mellitus after adult heart transplantation and the risk of renal dysfunction or mortality. *Transplantation*, 106(1):178-187. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33496556/

- Retrospective analysis using ISHLT Thoracic Organ Transplant Registry. Among 26,263 eligible subjects, 21% had new-onset post-HT DM within 5 years of HT. Post-HT DM was associated with increased risk of severe renal dysfunction and death or retransplantation compared to patients without post-HT DM.

Black RJ, et al. (2021). Swallowing and laryngeal complications in lung and heart transplantation: Etiologies and diagnosis. *J Heart Lung Transplant*, 40(12):1483-1494. Retrieved from: https://doi.org/10.1016/j.healun.2021.08.006

- Review article that discusses normal swallowing and vocal function and how oropharyngeal dysphagia and dysphonia may occur after heart and lung transplants. Proposed etiologies are ICU acquired weakness, intubation, GERD, neurologic changes, medications, laryngeal nerve injury, and respiratory factors. There is also discussion about how swallowing and laryngeal dysfunction impacts patient care and outcomes.

Jeon J, et al. (2021). Prognostic factors of renal outcomes after heart transplantation: A nationwide retrospective study. *J Clin Med*, 10(21):5110. Retrieved from: https://doi.org/10.3390/jcm10215110

- Multicenter retrospective cohort study of adult heart transplant recipients that sought to analyze predictive factors for renal outcomes after heart transplant. A total of 654 patients out of 736 transplanted survived until discharge of the index admission and were included in the study. Twelve (1.8%) patients developed ESKD over a median follow up period of 2.8 years. Factors associated with the development of ESKD were: perioperative RRT > 21 days (HR 8.64 CI 3.17-23.17, p<0.001), use of inotropes/vasopressors (HR 6.98, CI 2.10-23.17 p<0.002), and no use of ACEi/ARB (HR 0.24 CI 0.08-0.71, p=0.08). Of the 654 patients, 561 did not have pre-existing CKD and 104 (18.5%) of these patients were newly diagnosed with CKD over a median follow up period of 2.3 years. Factors associated with the development of CKD were: old age (HR 1.03 CI

1.01–1.05, $p < 0.01$), ECMO (HR 1.54 CI 1.14–2.07, $p < 0.01$), and RRT (1–21 days of RRT: HR 1.76 CI 1.28–2.41; and >21 days of RRT: HR 3.69 CI 1.41–9.68). In-hospital mortality was associated with: pre-existing renal disease (15.0% survival vs. 28.1% death, p = 0.01), more mechanical ventilation (24.6% vs. 86.0%, p <0.001), use of ECMO (21.6% vs. 61.4%, p <0.001), more RRT (22.5% vs. 91.8%, p <0.001), and less use of ACEi/ARB (32.3% vs. 15.8%, p = 0.01).

Venema CS, et al. (2021). Post-transplant inotrope score is associated with clinical outcomes after adult heart transplantation. *Clin Transplant*, 35(8):e14347. Retrieved from: https://doi.org/10.1111/ctr.14347

- Single center retrospective study aiming to determine if inotrope use impacted post-transplant outcomes. The population was divided into three different cohorts based on their inotrope score after heart transplant (higher inotrope score = higher use of inotropes): group one: 2.1 to 12.4, group two: 12.5 to 24.4, and group three: 24.5 to 75.6. More patients in the third group required extracorporeal life support (ECLS) (11.1% vs. 3.7% vs. 29.6%, respectively) and CVVH (11% vs 41% vs 78%). Mortality was not significantly different between the three groups at 30-days (p=0.43), 1-year (p=0.18), and 5-years (p=0.23). ICU length of stay was significantly shorter between the first and second groups (4.0 days vs. 8.5 days, p < 0.01) and between the first and third groups (4.0 days vs. 14.0 days, p < 0.01).

Duerinckx N, et al. (2021). Depressive symptoms at 1 year after surgery increase the risk of cardiac allograft vasculopathy and mortality in heart transplant recipients: A prospective cohort study. *Gen Hosp Psychiatry*, 71:20-26. Retrieved from: https://doi.org/10.1016/j.genhosppsych.2021.03.008

- Single center prospective cohort study to determine if post-transplant outcomes of cardiac allograft vasculopathy (CAV) and mortality are related to depressive symptoms at 1-year after heart transplant. Of the 190 patients assessed, 23.7% had depressive symptoms (17.9% mild, 4.7% moderate, 1.1% severe). On Cox regression analysis, presence of depressive symptoms was associate with increased mortality risk (HR 2.52 CI 1.35-4.71, p=0.004) and each 6 point increase in BDI was associated with a 31% increased mortality risk. Presence of depressive symptoms was associated with increased risk of CAV (HR 2.25 CI 1.01-4.98).

Roest S, et al. (2021). Influence of renal insufficiency pre-heart transplantation on malignancy risk postheart transplantation. *ESC Heart Fail*, 8(3):2172-2182. Retrieved from: https://doi.org/10.1002/ehf2.13309

- Single center retrospective cohort study to determine if the duration of heart failure and CKD pre-transplant impacts the risk of malignancy post-transplant. Duration of HF was not associated with an increased risk of malignancy on multivariable analysis (HR 1.03 CI 0.97-1.10, p = 0.28). Presence of CKD prior to transplant was associated with an increased risk of developing malignancy (HR 2.17 CI 1.24-3.82, p=0.007). Cumulative incidence of malignancies was 11.8% at 5-years, 28.4% at 10-years, and 40.3% at 15-years with the most common type of malignancy being skin malignancies (81%), followed by lung malignancies (5%), PTLD/lymphoma/leukemia (3%), and gastrointestinal (3%).

Nair N, et al. (2021 Mar). Risk prediction model for cutaneous squamous cell carcinoma in adult cardiac allograft recipients. *World J Transplant*, 11(3):54-69. Retrieved from: https://doi.org/10.5500/wjt.v11.i3.54

- Multicenter retrospective cohort study of the UNOS registry (n=23,736) seeking to identify risk factors and predict the incidence of cutaneous squamous cell carcinoma (cSCC) after heart transplant. A total of 1,827 (7.70%) patients developed cSSC. Risk factors associated with increased risk of the development of cSSC on multivariate analysis include older age (p<0.001), male sex (p<0.001), Caucasian race (p<0.001), HLA mismatch level (p=0.043), current malignancy at listing (p<0.001), and induction with OKT3 (p=0.006) or daclizumab (p<0.001). Patients with cSCC had an increased mortality risk compared to the non-cSCC group (HR 1.51 CI 1.25-1.82).

Barghash MH, et al. (2020). Recombinant herpes zoster vaccine after heart transplantation: A single center experience. *J Heart Lung Transplant*, 39(12):1501-1503. Retrieved from: https://doi.org/10.1016/j.healun.2020.09.001

- Single center retrospective cohort study to assess the clinical safety and efficacy of the Shingrix vaccine after heart transplant (n=65). All patients had a prior varicella infection shown by positive antibody titers. Average time to vaccine administration was 11.4 +/- 6.6 years. Forty-two (70.8%) patients received both doses of Shingrix. Adverse effects occurred in 35% of the patients after the first Shingrix vaccine, and 28% experienced adverse effects after the second Shingrix vaccine. There were no episodes of rejection after Shingrix vaccination. One patient developed a herpes zoster infection 2 months after the first dose of Shingrix.

Rolid K, et al. (2020). Long-term effects of high-intensity training vs moderate intensity training in heart transplant recipients: A 3-year follow-up study of the randomized-controlled HITTS study. *Am J Transplant*, 20(12):3538-3549. Retrieved from: https://doi.org/10.1111/ajt.16087

- Sixty-two patients were randomized and followed for 3 years to determine if high-intensity interval training (HIT) or moderate intensity continuous training (MICT) better impacted peak oxygen consumption (VO_{2peak}) after heart transplant. At 3 years, there was no significant difference between the two groups with regard to mean VO_{2peak} (24.0 mL/kg/min vs 24.1 ml/kg/min, p=0.163). The aerobic threshold increased significantly higher in the HIT group compared to the MICT group at the 3 year follow-up (1.35 L/min vs 1.22 L/min, p = 0.024).

Wang TJ, et al. (2020). Long-term outcomes and risk factors of renal failure requiring dialysis after heart transplantation: A nationwide cohort. *J Clin Med*, 9(8):2455. Retrieved from: https://doi.org/10.3390/jcm9082455

- Multicenter retrospective cohort study of heart transplant recipients in Taiwan (n=1129) to determine the incidence, association with long-term mortality, and risk factors associated renal failure requiring dialysis after heart transplant. A total of 321 (28.4%) patients developed renal failure requiring dialysis with a mean time from transplant of 3.4 +/- 3.2 years. One-year, three-year, and five-year mortality rates from any cause were all higher in the dialysis group compared to the non-dialysis group with hazard ratios ranging from 3.44 to 5.89 ($p<0.001$ for all). Predictors for renal failure requiring dialysis were HBV infection (OR 3.2 CI 0.14-0.76), pretransplantation diabetes (OR 1.5 CI 1.07-2.11), preexisting CKD (OR 2.65 CI 1.46-4.79), history of AKI (OR 2.36 CI 1.27-4.41), and primary HT diagnosis of CAD (OR 10.07 CI 6.33-18.4).

Punnoose LR, et al. (2020). Pregnancy outcomes in heart transplant recipients. *J Heart Lung Transplant*. 39(5):473-480. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/32201090/

- Observational study of the outcomes of heart transplant recipients included in the Transplant Pregnancy Registry, which is a voluntary international registry. Ninety-one female heart transplant recipients with 157 pregnancies were included. The average time from transplant to conception was 7 +/- 6.1 years. Successful births occurred in 69% pregnancies, and there were no neonatal deaths. Miscarriages occurred in 63% of pregnancies with MPA exposure vs 17% in pregnancies without MPA exposure.

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

- Double-blind, randomized clinical trial to determine the effectiveness of desmopressin on the amount of bleeding and transfusion requirements of patients undergoing heart transplant surgery. Forty-eight patients were randomized to either the desmopressin group or control group (normal saline). Compare to the control group after transplant, the desmopressin group had less chest tube drainage (411 +/- 48 mL vs 495 +/- 65mL, p=0.037) and less transfusion requirements (2+/- 0.7 units vs 4.2 +/- 0.9 units, p=0.41).

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

- Case report of the use of teriparatide to treat low-turnover bone disease in a heart transplant recipient. After one year of treatment, improvement in structural indices of osteoid wall thickness,

trabecular thickness, and trabecular number. Bone mineral density was stable and no new vertebral fractures occurred.

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

- Review article describing the pathophysiology and treatment of hypertension in patients after cardiac transplantation.

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://pubmed.ncbi.nlm.nih.gov/27743576/

- Large single-center cohort of 461 HT recipients to determine the role of heart rate and beta blockers as predictors of long-term mortality. By the end of the study, 36% of recipients were on a beta blocker at some time and this population had a lower mortality (HR 0.70 CI 0.49-0.99, p <0.05). Higher heart was associated with increased mortality (HR 1.02 CI 1.008-1.035, p=0.02).

Wang YJ, et al. (2016). Malignancy after heart transplantation under everolimus versus mycophenolate mofetil immunosuppression. *Transplant Proc*, 48(3):969-73. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/27234781/

- Retrospective analysis of 454 heart transplant recipients that received MMF (n=232) or EVR (n=222) after transplant and sought to determine the factors predicting malignancy. A total of 27 cancers were diagnosed after transplant (MMF=23, EVR=4), with the three most common being lymphoma, skin cancer, and prostate cancer. The 5- and 10-year survival rates for those with malignancies on MMF were 63.10% and 51.51% vs 69.06% and 66.40% for those on EVR.

Alvarez-Alvarez RJ, et al. (2015) Venous thromboembolism in heart transplant recipients: incidence, recurrence and predisposing factors. *J Heart Lung Transplant*. 34(2):167-74. Retrieved at: https://pubmed.ncbi.nlm.nih.gov/25434523/

- Single center observational study to describe the cumulative incidence and recurrence risk of VTE in 137 heart transplant recipients. Over a median follow-up of 8.4 years (3.3-13.2 years), the incidence rate of VTE was 12.7 episodes per 1,000 patient-years. Incidence rates were higher in the first year post-transplant (45.1 CI 28.9-67.1) than after the first year (8.7 CI 6.2-11.2). Risk factors for VTE were older age (aHR 1.04 CI 1.01-1.08, p=0.017), chronic renal dysfunction (aHR 2.06 CI 1.01-4.23), obesity (aHR 1.88 CI 1.001-3.52, p=0.050), and use of mTOR inhibitors (aHR 1.87 CI 1.07-3.27, p=0.029).

5.10 Miscellaneous Review Articles

Fraser M, et al (2024). Pharmacotherapy in the heart transplant recipient: A primer for nurse clinicians and pharmacists. *Clin Transplant*. 38(2):e15252. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38341767/

- Review of immunosuppression management post-heart transplant including agent-specific considerations, outcomes data, guideline recommendations, medical prophylaxis, and adherence.

Demiralp G, et al (2024). Heart Transplantation-Postoperative Considerations. *Crit Care Clin*. 40(1):137-157. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37973350/

- Overview of post-operative management of heart transplant recipients including system-based complications and considerations, differences in management compared to other cardiac surgery patients, and coordination of care across multidisciplinary teams.

Chrysakis, N et al. (2024). Heart Transplantation. *Journal of clinical medicine*, 13(2), 558. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38256691/

- An overview of current issues in heart transplantation, covering topics ranging from HLA compatibility to marginal donors to novel immunosuppression therapies

Nesseler N, et al (2023). Perioperative Management of Heart Transplantation: A Clinical Review. *Anesthesiology*. 2023;139(4):493-510. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37458995/

- Review of perioperative considerations and management immediately post-heart transplant, including hemodynamic management, primary graft dysfunction, right heart failure, arrhythmias, tricuspid regurgitation, immunosuppression, rejection, infections, hemostasis, mechanical ventilation, acute kidney injury, and nutrition.

Alamouti-Fard E, et al. (2022). Normothermic Regional Perfusion is an Emerging Cost-Effective Alternative in Donation After Circulatory Death (DCD) in Heart Transplantation. *Cureus*, 14(6), e26437. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35800191/

- Overview of normothermic regional perfusion and how it can expand the donor pool for thoracic transplant candidates and DCD donors

Villegas-Galaviz J, et al. (2022). Clinical outcomes of heart transplantation using hepatitis c-viremic donors: A systematic review with meta-analysis. *J Heart Lung Transplant*, S1053-2498(22)00015-8. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35153130/

- A systematic review with meta-analysis that evaluated outcomes of heart transplantation from hepatitis C virus (HCV)-viremic donors to nonviremic recipients. The HCV-transmission rate was >97%, but the cure rate was 100% with direct-acting antiviral (DAA) therapy. The 6 and 12-month survival were 95.6% and 92.9% respectively with no deaths associated with HCV infection.

Coniglio AC, et al. (2021). Innovations in heart transplant: A review. *J Card Fail*, S1071-9164(21):00437-1. Retrieved from: https://doi.org/10.1016/j.transproceed.2021.08.048

- Mainly discusses expansion in the donor pool by the addition of donation after cardiac death (DCD) donors and hepatitis C positive donors, as well as how donor-recipient matching and post-transplant care have improved outcomes.

Guerroro-Miranda CY and Hall SA. (2021). Rethinking the future with evolving technology: It's time to empower change in heart transplantation. *Am J Transplant*, 21(2):453-455. Retrieved from: https://doi.org/10.1111/ajt.16221

- Review article discussing how biomarkers may be used to identify patients at higher risk for events like rejection after heart transplantation.

Loungani RS, et al. (2020). Biomarkers in advanced heart failure: Implications for managing patients with mechanical circulatory support and cardiac transplantation. *Circ Heart Fail*, 13(7):e006840. Retrieved from: https://doi.org/10.1161/circheartfailure.119.006840

- Review article discussing traditional and newer biomarkers in both patients with LVADs and patients receiving a heart transplant. It discusses how these biomarkers may be used in clinical practice to improve patient care and outcomes.

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

- A review of recently published literature in heart transplant