

8. Additional organ-specific considerations

8.1 Cardiac allograft vasculopathy (CAV)

8.2 Cardiovascular risk management

8.3 Post-transplant diabetes mellitus

8.4 Biliary complications and management

8.5 Calcineurin inhibitor neurotoxicity

8.6 Chronic allograft nephropathy/interstitial fibrosis and tubular atrophy

8.7 Hemolytic uremic syndrome (HUS)/Thrombotic thrombocytopenic purpura (TTP)

8.8 Bone and mineral disorder management

8.1. Cardiac allograft vasculopathy (CAV)

D'Addese L, et al. (2023). Early aspirin use and the development of cardiac allograft vasculopathy in pediatric heart transplant recipients: A pediatric heart transplant society analysis. *J Heart Lung Transplant.* 42(1):115-123. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/36328858/>

- Retrospective study of 3,011 pediatric heart transplant recipients who survived 3 or more years without evidence of CAV were included from the Pediatric Heart Transplant Society database
- Aspirin use varied widely and early aspirin use was not associated with a reduction in risk of CAV or graft loss

Laks JA, et al. (2022). Cardiac allograft vasculopathy: A review. *Laks JA, Dipchand AI. Pediatr Transplant.* 26(3):e14218. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34985793/>

- A review of the literature regarding CAV in the adult and pediatric heart transplant populations was conducted via a search of the Medline and Embase databases.
- Medications such as statins have been shown to be beneficial in slowing the development of CAV. Other medications include those used as induction therapy, mycophenolate mofetil and mTOR inhibitors.

Choi HI, et al. (2022). Long-term efficacy of everolimus as de novo immunosuppressant on the cardiac allograft vasculopathy in heart transplant recipients. *Atherosclerosis.* Sep;357:1-8. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35981436/>

- 107 heart transplant recipients between 2005 and 2015 were retrospectively reviewed to determine the long-term safety and efficacy of everolimus as a de novo immunosuppressant therapy for CAV progression.
- De novo use of everolimus in combination with reduced dose calcineurin inhibitor was associated with reduced progression of CAV to 5 years after heart transplant, and was found to be safe and well-tolerated. Everolimus was not associated with significantly different all-cause mortality, graft failure, re-transplantation, and treatment requiring rejection for 8 years of follow-up.

Ellimuttill TM, et al. (2021). Effect of Statin Intensity on the Progression of Cardiac Allograft Vasculopathy. *Fail Rev.* 12;7:e15. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34950505/>

- Single-center retrospective study of 143 heart transplant recipients evaluating the effect of statin use and intensity on cardiac allograft vasculopathy (CAV).
- CAV-free survival did not differ between the two statin intensity groups, with a mean CAV-free survival of 48.5 and 46.1 months in the low- and moderate-/high-intensity statin groups, respectively (p=0.435).
- Median post-transplant LDL was not associated with time to CAV (p=0.790).
- The study suggests that advancing to moderate- or high intensity statin after heart transplant may not provide additional long-term clinical benefit.

Bergmark BA, et al. (2021). Early aspirin use, allograft rejection, and cardiac allograft vasculopathy in heart transplantation. Bergmark BA, Zelniker TA, Kim M, Mehra MR, Stewart GC, Page DS, Woodcome EL, Givertz MM. Clin Transplant. 35(10):e14424. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34254366/>

- Retrospective observational cohort study of 120 heart transplant recipients analyzing the impact of early aspirin administration on moderate to severe CAV.
- Patients were categorized by rejection status (AMR or ACR) and early ASA use. Early ASA was defined as use of ASA for a minimum of 6 months in the first year following transplant.
- In patients with ACR or AMR, ASA therapy was associated with significantly lower rates of CAV ($P = .001$). No difference was seen in the rates of CAV in patients without rejection.
- The study concluded that early ASA use after OHT was associated with lower rates of moderate to severe CAV only in those patients with episodes of allograft rejection.

Asleh R, et al. (2021). Association of Aspirin Treatment With Cardiac Allograft Vasculopathy Progression and Adverse Outcomes After Heart Transplantation. 27(5):542-551. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33962742/>

- Retrospective review of 529 heart transplant recipients evaluating the association of aspirin with CAV.
- Aspirin was administered in 74 patients within the first year after transplant and in 122 patients after the first year. 333 patients did not receive aspirin. The median time from transplant to aspirin initiation was 0.12 years and 5.04 years for the early and late users, respectively. The median overall follow up time in all of the groups was 6.7 years.
- Plaque volume and plaque index were significantly reduced in patients who received early aspirin ($P = .007$ and $P = .002$, respectively). The composite of all CAV-related events was not significantly different between the groups ($P = .16$).

Aleksova N, et al. (2021). Low-Density Lipoprotein Cholesterol Level Trends and the Development of Cardiac Allograft Vasculopathy After Heart Transplantation. 16;3(12):1453-1462. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34993457/>

- Retrospective review of heart transplant recipients and the relationship between LDL and CAV.
- A total of 386 patients followed for a median of 4.4 years. There was no significant association between LDL and CAV at 1-year post-transplant adjusted odds ratio (OR) 1.00, 95% confidence interval (CI): 0.61, 1.63 for baseline LDL, and adjusted OR 1.25, 95% CI: 0.74, 2.10 for 1-year LDL-C.
- In conclusion, the study findings do not support targeting a specific LDL for CAV purposes for patients who do not otherwise meet criteria for guideline-recommended LDL target levels.

Alkesova N, et al. (2021). The effect of antiplatelet therapy on survival and cardiac allograft vasculopathy following heart transplantation: A systematic review and meta-analysis. Clin Transplant. 35,e14125. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33068308/>

- Systematic review and meta-analysis of seven observational cohort studies analyzing the effect of aspirin on cardiac allograft vasculopathy (CAV), all-cause mortality and CAV-related mortality after heart transplantation.
- There was no statistically significant difference in the incidence of CAV (RR 0.75; 95% CI, 0.44-1.29; $I^2=70\%$), all-cause mortality (HR 0.95; 95% CI, 0.67-1.34; $I^2=0\%$) and CAV-related mortality (HR 1.29; 95% CI, 0.66-2.56; $I^2=0\%$) after heart transplantation with aspirin compared to no aspirin.
- The study concludes that there is limited evidence that aspirin may reduce the development of CAV.

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, 626-35. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32558174/>

- Retrospective, single-center study of 137 patients investigating the prognostic value of proteinuria after conversion to sirolimus-based maintenance immunosuppression
- Change in plaque volume ($P < 0.001$) and plaque index ($P = 0.001$) were significantly higher among patients with proteinuria
- All-cause mortality ($P = 0.01$) was significantly higher with proteinuria but the risk of CAV-related events was similar ($P = 0.61$)
- The results suggest that heart transplant recipients who develop proteinuria after conversion to sirolimus are at higher risk of CAV progression and mortality

Madan S, Patel SR, Jorde UP. (2020). Cardiac allograft vasculopathy and secondary outcomes of hepatitis C-positive donor hearts at 1 year after transplantation [published online ahead of print, 2020 Jun 30]. *J Heart Lung Transplant*. S1053-2498(20)31623-5. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32680608/>

- Large cohort study evaluating CAV rates for hepatitis C-positive donors at 1 year for heart transplant recipients from January 2015 to September 2018
- Divided into 3 groups HCV Ab \pm / NAT+ ($n = 107$), HCV Ab+/NAT-($n = 69$), HCV ab-/NAT-($n = 6,943$)
- Rates of CAV at 1 year were similar in the 3 groups (HCV-naive 7.3%, HCV-viremic 10.4%, and HCV Ab+ non-viremic 7.3%, $p = 0.456$)
- Secondary outcomes including graft function, need for chronic HD, treated rejection rates, hospitalization for acute rejection or rejection at 1 year were similar amongst groups

Harris J, Teuteberg J, Shullo M. (2018). Optimal low-density lipoprotein concentration for cardiac allograft vasculopathy prevention. *Clin Transplant*. 32(5):e13248. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/29603413/>

- Retrospective cohort analyzing the risk of developing CAV with respect to different LDL goals
- CAV developed in 12/37 (32.4%) patients with LDL ≥ 100 mg/dL vs 25/157 (15.9%) in patients with LDL < 100 mg/dL ($p = 0.021$). Study also found a delay to CAV with LDL < 100 mg/dL.
- The results of this study suggests a goal of LDL < 100 mg/dL in heart transplant recipients is reasonable to help prevent CAV development.

Peled Y, et al. (2017). Early aspirin initiation following heart transplantation is associated with reduced risk of allograft vasculopathy during long-term follow-up. *Clin Transplant*. 31: e13133. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28990263>

- Retrospective study of 206 heart transplant patients to evaluate the association between early aspirin therapy and long-term risk of CAV.
- Early aspirin use was associated with a statistically significant reduction in CAV risk of 84%.

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/26820618>

- A total of 110 of 115 patients completed the 12-month SCHEDULE study as described above and 102 attended a follow-up visit at month 36.
- Coronary intravascular ultrasound at 36 months revealed significantly reduced progression of allograft vasculopathy in the everolimus group compared with the CNi group, as defined by a significantly lower mean increase in maximal intimal thickness from week 7-11 ($p = 0.019$).
- Biopsy-proven acute rejection grade $\geq 2R$ occurred in 10.2% and 5.9% of everolimus- and calcineurin inhibitor-treated patients, respectively, during months 12-36. Serious adverse events occurred in 37.3% and 19.6% of everolimus- and calcineurin inhibitor-treated patients, respectively ($p = 0.078$).

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): e002252. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/?term=azarbal+and+inductio>

- Retrospective study of heart transplant patients between 2010 and 2012 who received either induction with antithymocyte globulin or no induction therapy. Primary endpoints were first year plaque progression and incidence of rapid plaque progression.
- Overall CAV progression was slower in those patients who received induction with antithymocyte globulin in terms of maximal intimal thickness, maximal percent stenosis, and plaque volume on IVUS.

Watanabe T, et al. (2016). Suppressive effects of conversion from mycophenolate mofetil to everolimus for the development of cardiac allograft vasculopathy in maintenance of heart transplant recipients. *Int J Cardiol.* 203: 307 – 14. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/26523360>

- Retrospective review of 63 heart transplant recipients who survived at least at 1 year after heart transplant. Twenty-four recipients were converted from mycophenolate mofetil (MMF) to everolimus (EVL) (EVL group, 2.2 ± 2.3 years after heart transplant), while 39 recipients were maintained on MMF (MMF group, 2.4 ± 2.2 years after heart transplant). The EVL group underwent three-dimensional intravascular ultrasound analysis before and 1 year after conversion to EVL and these data were compared with data from 2 consecutive IVUS in the MMF group.
- IVUS indices in the EVL group at 1 year after conversion did not show increased CAV development, whereas a significant increase in %plaque volume (p=0.006) and decrease in lumen volume (p<0.001) were observed in the MMF group. EVL conversion was significantly associated with smaller increases in %plaque volume (p=0.004) and smaller decreases in lumen volume (p=0.017). IVUS indices in the late EVL conversion group (≥ 2 years) also did not exhibit increased CAV development while those in the MMF group did.

Sieg A, et al. (2016). Statin therapy in cardiac allograft vasculopathy progression in heart transplant patients: does potency matter? *Transplant Rev (Orlando)*, 30(3): 178-86. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/27079752>

- This literature review focuses on risk factors and pathophysiology of CAV, treatment options, and specifically the role of statin therapy at varying intensity levels.

Guethoff S, et al. (2015). De novo sirolimus with low dose tacrolimus versus full dose tacrolimus with mycophenolate mofetil after heart transplantation- 8 year results. *J Heart Lung Transplant.* 34(5): 634-42. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/25701373>

- Heart transplant recipients between 1998 and 2005 were randomized to two groups: low dose tacrolimus with sirolimus or tacrolimus with mycophenolate mofetil. At 8 years there was no statistically significant difference in number of acute rejection episodes, survival, or CAV.
- Freedom from CAV grade 1 or higher was 55.4% in the low dose tacrolimus/sirolimus group compared to 60% in the tacrolimus/mycophenolate mofetil group.

Hollis IB, Reed BN, Moranville MP. (2015). Medication management of cardiac allograft vasculopathy after heart transplantation. *Pharmacotherapy*, 35(5): 489 – 501. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/26011142>

- A review of the literature regarding medication management of CAV was conducted via a search of the MEDLINE database. Studies were included if they were published in English, conducted in humans ≥ 18 years of age or older, and used noninvestigational medications.
- Immunosuppressive medications such as the antiproliferative mycophenolate, the calcineurin inhibitor tacrolimus, and the proliferation signal inhibitors sirolimus and everolimus have been shown to prevent the development of CAV.
- Certain cardiovascular medications, such as HMG-CoA reductase inhibitors (statins), gemfibrozil, calcium channel blockers, and angiotensin-converting enzyme inhibitors, have also demonstrated efficacy.
- Prevention of CAV has also been observed with prophylaxis against cytomegalovirus infection and antioxidant medications. Despite being commonly used in heart transplant

patients, neither antiplatelet agents nor glycemic control have proved effective at preventing CAV. Only sirolimus has been shown to arrest the progress of existing CAV.

Arora S, et al. (2015). The effect of everolimus initiation and calcineurin inhibitor elimination on cardiac allograft vasculopathy in de novo recipients: One-year results of a Scandinavian randomized trial.

Am J Transplant. 15(7): 1967 – 75. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/25783974>

- A 12-month, open-label, multicenter, randomized, controlled Scandinavian study, in which adult de novo heart transplant recipients (n = 115) were randomized to everolimus (3-6 ng/mL) with reduced-exposure calcineurin inhibitor (CNI; cyclosporine) to weeks 7-11 after transplant, followed by increased everolimus exposure (target 6-10 ng/mL) with cyclosporine withdrawal or standard-exposure cyclosporine. All patients received mycophenolate mofetil and corticosteroids.
- Ninety-five (83%) patients had matched intravascular ultrasound examinations at baseline and 12 months. Mean (\pm SD) recipient age was 49.9 ± 13.1 years.
- The everolimus group (n = 47) demonstrated significantly reduced CAV progression as compared to the calcineurin inhibitor group (n = 48) (Δ Maximal Intimal Thickness 0.03 ± 0.06 and 0.08 ± 0.12 mm, Δ Percent Atheroma Volume 1.3 ± 2.3 and $4.2 \pm 5.0\%$, Δ Total Atheroma Volume 1.1 ± 19.2 mm³ and 13.8 ± 28.0 mm³ [all p-values ≤ 0.01]).
- Everolimus patients also had a significantly greater decline in levels of soluble tumor necrosis factor receptor-1 as compared to the calcineurin inhibitor group (p = 0.02).

Shuchita Gupta MD (2014). Drugs for the Prevention and Treatment of Cardiac Allograft Vasculopathy. Cardiol Pharmacol 3:123. Retrieved from:

https://www.researchgate.net/publication/283748778_Drugs_for_the_Prevention_and_Treatment_of_Cardiac_Allograft_Vasculopathy

- This review discusses the currently available drugs for CAV, the evidence behind their use, and future targets of therapy.

Eisen HJ, et al. (2013) Everolimus versus mycophenolate mofetil in heart transplantation: a randomized, multicenter trial. Am J Transplant. 13(5): 1203-16. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/23433101>

- Randomized, prospective, multicenter study comparing the efficacy, safety and incidence of CAV in de novo heart transplant patients receiving everolimus (1.5 mg/day with goal trough 3-8 ng/mL or 3 mg/day with goal trough 6-12 ng/mL in divided doses) with reduced-dose cyclosporine vs. mycophenolate mofetil with full-dose cyclosporine (intervention initiated within 72 hours of transplantation).
- Results: Everolimus at a target concentration of 3-8 ng/mL had the following outcomes: noninferior to mycophenolate mofetil for the composite outcome of biopsy-proven acute rejection of ISHLT grade $\geq 3A$, acute rejection with hemodynamic compromise, graft loss/re-transplantation, death, or loss to follow-up at 12 months and was maintained at month 24; significantly reduced intimal proliferation on blinded IVUS assessment and significantly less patients diagnosed with CAV during the first year post-transplant. There was a higher mortality rate in patients receiving everolimus 3 mg (target 6–12 ng/mL), leading to discontinuation of recruitment to this treatment arm.

Masetti M, et al. (2013) Differential effect of everolimus on progression of early and late cardiac allograft vasculopathy in current clinical practice. Am J Transplant. 3(5): 1217-26. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pubmed/23621161>

- Prospective, observational cohort study with 143 heart transplant recipients. The early cohort included 91 patients with baseline (within 6 weeks of transplant) and 1 year follow-up IVUS study. The late cohort included 52 patients with 1 year and 5 year IVUS studies. Patients received either everolimus + cyclosporine + steroids vs. cyclosporine + mycophenolate mofetil + steroids.
- In the early cohort, patients could be started on everolimus (goal trough 3-8 ng/ml) within a few days after transplant or after 2-6 weeks of mycophenolate mofetil therapy post-

transplant in combination with cyclosporine. In the late cohort, patients could switch from mycophenolate mofetil/azathioprine to everolimus in combination with cyclosporine after the year 1 IVUS.

- In the early cohort, everolimus independently reduced the odds for early CAV (0.14 [0.01–0.77]; $p = 0.02$). However, everolimus did not influence late CAV progression.

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(5): 708-20. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/22207715>

- Retrospective analysis of sirolimus with calcineurin inhibitor withdrawal vs. continued calcineurin inhibitor therapy for the long-term attenuation of CAV progression and effects on cardiac-related morbidity and mortality. The time from transplant to conversion to sirolimus and calcineurin inhibitor withdrawal ranged from 0.2-9 years.
- Results: Substituting calcineurin inhibitor with sirolimus <2 years post-transplant resulted in a delay in progression of plaque volume and a delay in progression of plaque index. Those converted to sirolimus > 2 years post-transplant had a significant increase in vessel volume, resulting in a delay in progression of plaque index as well. Five year survival and freedom from cardiac-related events was significantly improved in those on sirolimus.

Arora S, et al. (2011) Effect of everolimus introduction on cardiac allograft vasculopathy – results of a randomized, multicenter trial. *Transplantation*. 92(2): 235-43.

Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/21677600>

- Multicenter, randomized, controlled-trial comparing the effect of everolimus + low-dose calcineurin inhibitor + mycophenolate mofetil/azathioprine on CAV vs. standard calcineurin inhibitor + mycophenolate mofetil/azathioprine therapy.
- Results revealed no significant influence on CAV progression during the 12-month follow-up period which was assessed by intravascular ultrasound.
- However, a significant reduced rate of CAV progression was seen in patients treated with everolimus + low-dose calcineurin inhibitor + azathioprine vs. standard calcineurin inhibitor + azathioprine. On the other hand, an accelerated rate of CAV progression was seen among patients treated with everolimus + low-dose calcineurin inhibitor + mycophenolate mofetil vs. standard calcineurin inhibitor + mycophenolate mofetil.

Tremmel JA, et al. (2011) Comparison of drug-eluting versus bare metal stents in cardiac allograft vasculopathy. *Am J Cardiol*. 108(5): 665-8. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/21684511>

- Retrospective analysis of consecutive cardiac transplantation patients at a single-center who received a drug-eluting (DES) vs. bare-metal stent (BMS) for de novo cardiac allograft vasculopathy from 1997-2009. Angiographic and clinical outcomes were subsequently evaluated at 1 year.
- Results: At the 12-month angiographic follow-up visit, the mean lumen loss was significantly lower in the DES group vs. BMS group (0.19 ± 0.73 mm vs 0.76 ± 0.97 mm, $p=0.02$). The DES group had a lower rate of in-stent restenosis (12.5% vs. 33%, $p=0.18$) as well as a significantly lower rate of target lesion revascularization (0% vs. 19%, $p=0.03$). Additionally, at one year DESs were associated with a lower composite rate of cardiac death and nonfatal MI (12% vs. 38%, $p=0.04$).
- Conclusion: DESs are safe and effective in the suppression of neointimal hyperplasia after PCI for CAV, resulting in significantly lower rates of late lumen loss and target lesion revascularization, as well as a reduced combined rate of cardiac death and nonfatal MI.

Mehra MR, et al. (2010) International Society for Heart and Lung Transplantation working formulation of a standardized nomenclature for cardiac allograft vasculopathy – 2010. *J Heart Lung Transplant*.

29(7): 717-27. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/20620917>

- Clinical consensus guidelines derived from critical analysis of available literature pertaining to angiography, intravascular ultrasound imaging, non-invasive imaging tests, and gene-based and protein-based biomarkers for standardizing the nomenclature for CAV.

Costanzo MR, et al. (2010) The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. *J Heart Lung Transplant.* 29(8): 914-56.

Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/20643330>

- Guidelines published by ISHLT on the care of heart transplant patients.
- Specific pages: 934 and 935 – outlines recommendations on the diagnosis and management of cardiac allograft vasculopathy; 942 – outlines recommendations on re-transplantation.

Aqel RA, et al. (2008) Re-stenosis after drug-eluting stents in cardiac allograft vasculopathy. *J Heart Lung Transplant,* 27(6): 610-5. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/18503959>

- Retrospective analysis of patients who received at least one drug-eluting stent for a previously untreated coronary lesion to examine the re-stenosis rates.
- Results: Drug-eluting stents have a favorable outcome when used in heart transplant patients for the treatment of CAV. Re-stenosis rates were 18%, 21%, and 26% at 6, 9 and 12 months, respectively. Predictors of re-stenosis included non-white race, ischemic etiology, intervention precipitated by symptoms and severe stenosis ($\geq 90\%$ stenosis) of the target lesion.

Kobashigawa JA, et al. (2005) Ten-year follow-up of a randomized trial of pravastatin in heart transplant patients. *J Heart Lung Transplant.* 24(11): 1736-40.

Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/16297773>

- A ten-year follow-up of the original study (*N Engl J Med* 1995).
- Results: The use of pravastatin in heart transplant patients maintains survival benefit and appears to reduce the development of CAV. Increased 10-year survival with the pravastatin group (68% pravastatin vs. 48% control; $p=0.026$). 10-year freedom from angiographic CAV and/or death was greater in the pravastatin group (43% vs. 20%; $p=0.009$).

Kobashigawa JA, et al. (2005) Multicenter intravascular ultrasound validation study among heart transplant recipients: outcomes after 5 years. *J Am Coll Cardiol.* 45(9): 1532-7.

Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/15862430>

- Multicenter study to assess the validity of first-year IVUS data as a surrogate marker for long-term outcome after heart transplantation. First-year IVUS results and subsequent five-year clinical follow-up data were reviewed in 125 heart transplant patients. The change in maximal intimal thickness (MIT) from baseline to one-year was recorded into two groups: those with ≥ 0.5 mm (group 1) and those with MIT < 0.5 mm (group 2).
- Results: Group 1 compared to group 2 had a higher incidence of death or graft loss (20.8% vs. 5.9%, $p=0.007$), had more nonfatal major adverse cardiac events and/or death or graft loss (45.8% vs. 16.8%; $p=0.003$), and had more findings of newly occurring angiographic luminal irregularities (65.2% vs. 32.6%, $p=0.004$).
- This study suggests that progression of intimal thickening ≥ 0.5 mm in the first year after transplantation appears to be a reliable surrogate marker for subsequent mortality, nonfatal major adverse cardiac events, and development of angiographic CAV through 5 years after heart transplant.

Keogh A, et al. (2004) Sirolimus in de novo heart transplant recipients reduces acute rejection and prevents coronary artery disease at 2 years: a randomized clinical trial. *Circulation,* 110(17): 2694-700.

Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/15262845>

- Randomized, open-label study comparing sirolimus with azathioprine in combination with cyclosporine and steroids at the time of transplant on acute cellular rejection and graft vasculopathy in heart transplant.
- Results: Sirolimus used from the time of transplant markedly reduced the proportion of patients experiencing acute rejection (32.4% 3 mg/day sirolimus vs. 56.8% azathioprine; $p=0.027$) with comparable patient survival at a dose of 3 mg/day. At 6 months and 2 years, patients on azathioprine had significantly increased measurements of all CAV parameters (mean and maximal intima+media thickness) and a significantly higher incidence of CAV compared to sirolimus.

Mancini D, et al. (2003) Use of rapamycin slows progression of cardiac transplantation vasculopathy. *Circulation*, 108(1): 48-53. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/12742978>

- Open-label, prospective, randomized study investigating the efficacy of rapamycin in preventing disease progression in patients with angiographically documented transplantation vasculopathy versus standard care (calcineurin inhibitor, antiproliferative, and steroids).
- The primary end point was a composite of clinically significant events including death, acute myocardial infarction, need for angioplasty or bypass surgery and/or a >25% increase in the catheterization score.
- Results: In the rapamycin group, 3/22 patients reached primary end points versus 14/24 patients in the control group ($P<0.001$). Rapamycin effectively slowed the progression of graft vasculopathy and reduced the incidence of clinically significant cardiac events.

Wenke K, et al. (2003) Simvastatin initiated early after heart transplantation: 8-year prospective experience. *Circulation*, 107(1): 93-7. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/12515749>

- Prospective, randomized, unmasked study comparing the efficacy of simvastatin (started on POD#4) with dietary therapy alone. After 4 years, most patients in both groups received statins due to improved survival and lower incidence of transplant vasculopathy.
- Results: At 8 years, survival rates were 88.6% in simvastatin group vs. 59.5% in control group ($p<0.006$). Incidence of transplant vasculopathy confirmed by angiography was 24.4% in the simvastatin group vs. 54.7% in the control group ($p<0.02$).

See VY Jr, et al. (2003) Effect of atorvastatin on postcardiac transplant increase in low-density lipoprotein cholesterol reduces development of intimal hyperplasia and progression of endothelial dysfunction.

Am J Cardiol. 92(1): 11–5. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/12842237>

- Patients were randomized to control ($n = 13$) or to 10 to 20 mg of atorvastatin ($n = 12$). Four patients in the control group had an LDL > 130 mg/dl and niacin was given. At the 1 year intracoronary ultrasonography, patients taking atorvastatin showed a decrease in new or progressing lesions (2.5 ± 1.7 vs. 4.2 ± 1.8 lesions/patient, $p = 0.02$), progression of maximal intimal thickness (0.12 ± 0.07 vs. 0.52 ± 0.17 mm, $p = 0.04$), and percent area stenosis ($5.9 \pm 2.2\%$ vs. $19.0 \pm 5.5\%$, $p = 0.04$).
- Atorvastatin administered to patients with normal or mild hypercholesterolemia in the initial year after transplant reduced the initial increase in LDL cholesterol. This in turn prevented the development and progression of coronary artery lesions and endothelial dysfunction with only mild long-term decreases in cholesterol levels.

Eisen HJ, et al. (2003) Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. *N Engl J Med*. 349(9): 847-58. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/12944570>

- Randomized, double-blind, prospective trial comparing everolimus + cyclosporine + corticosteroids with azathioprine + cyclosporine + corticosteroids in recipients of a first heart transplant. Interventions were initiated within 72 hours after transplant.
- Results: Both 1.5 mg/day and 3 mg/day of everolimus administered in combination with cyclosporine and corticosteroids were superior to azathioprine + cyclosporine + corticosteroids in preventing the primary efficacy endpoint (death, graft loss or a second

- transplantation, or biopsyproven rejection) at 6 months. Average increase in the maximal intimal thickness and incidence of CAV was significantly less in both everolimus groups compared to azathioprine containing group.

Kobashigawa JA, et al. (1995) Effect of pravastatin on outcomes after cardiac transplantation. *N Engl J Med.* 333(10): 621-7. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/7637722>

- Prospective, randomized, open-label trial assessing the effect of pravastatin on cholesterol lowering, rejection, survival, and the development of coronary vasculopathy in heart transplant patients.
- Results: Pravastatin (doses of 40 mg/day) lowers cholesterol levels; reduces the incidence of cardiac rejection with hemodynamic compromise, thereby increasing first-year survival (95% vs. 81 %; p=0.037); and reduces the development of coronary vasculopathy (3 pts vs. 10 pts; p=0.049).

8.2. Cardiovascular risk management

Mekraksakit P, et al. (2023). A Systematic Review and Meta-Analysis of Posttransplant Anemia with Overall Mortality and Cardiovascular Outcomes Among Kidney Transplant Recipients. *Progress In Transplantation.* 33(1):78-89. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/36591924/>

- Meta-analysis in adult kidney transplant recipients assessing the association between posttransplant anemia and post-transplant outcomes including cardiovascular mortality
- Posttransplant anemia was associated with overall mortality (pooled risk ratio = 1.72 [1.39, 2.13]), graft loss (pooled risk ratio = 2.28 [1.77, 2.93]), cardiovascular death (pooled risk ratio = 2.06 [1.35, 3.16]), and cardiovascular events (pooled risk ratio = 1.33 [1.10, 1.61])

Sommerer C, et al. (2023). Cardiovascular Outcomes in De Novo Kidney Transplant Recipients Receiving Everolimus and Reduced Calcineurin Inhibitor or Standard Triple Therapy: 24-month Post Hoc Analysis From TRANSFORM Study. *Transplantation.* Online ahead of print. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/36959121/>

- Post hoc analysis of TRANSFORM study, a 24-month prospective, open label trial in 2037 de novo kidney transplant recipients randomized 1:1 to receive either everolimus with low-dose CNI or mycophenolate with standard-exposure CNI
- Incidence of MACE (major adverse cardiac event) was similar between groups suggesting that everolimus with reduced dose CNI may be an alternative standard of care in kidney transplant recipients

Nassar M, et al. (2022). New onset hypertension after transplantation. *World J Transplant.* 12(3):42-54. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35433331/>

- Review of the prevalence, risk factors, etiology, complications, prevention, and management of hypertension after organ transplant.
- Summary of available studies regarding the pharmacologic management of posttransplant hypertension.
- Management of posttransplant hypertension relies on first-line therapies such as dihydropyridine calcium channel blockers which also effectively minimize calcineurin-induced vasoconstriction and beta-blocker use. ACE inhibitors are usually avoided during the first 2-6 months due to the risk of hyperkalemia, anemia and effect on renal function.

Aziz F, et al. (2022). New Approaches to Cardiovascular Disease and Its Management in Kidney Transplant Recipients. *Transplantation.* 106(6):1143-1158. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34856598/>

- Focused review on the limited evidence on cardiovascular events in kidney transplant recipients with specific focus on management of cardiovascular issues more prevalent among kidney transplant recipients such as pulmonary hypertension, valvular disease, and diastolic dysfunction.
- The use of new evolving drug classes for treatment of heart failure such as sacubitril-valsartan is also discussed with respect to this population.

Kuźmiuk-Glembin I, et al. (2022). Short-term Effects of Losartan on Cardiovascular Risk and Allograft Injury Biomarkers in Kidney Transplant Recipients. *Transplant Proc.* 54(4):981-988. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35346485/>

- Prospective, open-label, multi-center clinical trial (CELART) was performed to investigate the short-term effect of losartan on injury and the intrarenal fibrosis of the allograft as well as the influence of this treatment on cardiovascular risk biomarkers and the safety of the treatment in kidney transplant recipients.
- Patients enrolled to the trial were minimum 3 months after kidney transplant, with stable graft function (defined as estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m²) and with arterial hypertension.
- After 6 months of therapy there were no significant differences in changes of eGFR, albuminuria, hemoglobin and potassium concentrations, urine excretion of PIIINP, and TGF β -1 between groups. There was a trend in the L group to decrease the concentration of serum NT-proBNP.

Iannuzzo G, et al. (2022). Dyslipidemia in Transplant Patients: Which Therapy? *J Clin Med.* 11(14):4080. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35887846/>

- Increasing prevalence of cardiovascular disease has become the leading cause of death following kidney and heart transplant, and the second leading cause after liver transplant.
- Review on the distinct mechanisms of standard immunosuppressive agents such as corticosteroids, calcineurin inhibitors, antimetabolites, and mammalian target of rapamycin inhibitors and their effect on dyslipidemia and cardiovascular disease.
- Summary of available lipid lowering agents and a proposed treatment algorithm for post-transplant dyslipidemia considering potential drug interactions with concomitant immunosuppression.

Ueki K, et al. (2021). Development and validation of a risk score for the prediction of cardiovascular disease in living donor kidney transplant recipients. *Nephrol Dial Transplant.* 36,365-74. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33367750/>

- A single-center, derivation cohort study proposing a simple new score-based model for predicting cardiovascular disease in living donor kidney recipients and assessing its external validity

Charnaya O, Seifert M. (2021). Promoting cardiovascular health post-transplant through early diagnosis and adequate management of hypertension and dyslipidemia. *Pediatr Transplant.* 25, e13811. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32871051/>

- A review of the impact, risk factors, monitoring and management of hypertension and dyslipidemia in pediatric kidney transplant recipients.

Seeman T, Feber J. (2021). Should ACE inhibitors or calcium channel blockers be used for post-transplant hypertension? *Pediatr Nephrol.* 36,539-49. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32060819/>

- A review of available evidence of the use of CCB and ACE-I in renal transplant recipients.
- Proposes an algorithm for choice of CCB or ACE-I based on patient-specific factors

Kuhl M, et al. (2019). Treatment of hypercholesterolaemia with PCSK9 inhibitors in patients after cardiac transplantation. *14(1)*, e0210373. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6335020/>

- Retrospective study that investigated the use of PCSK9 inhibitors in heart transplant recipients with intolerance to statins or need for additional cholesterol reduction, as well as evidence of cardiac allograft vasculopathy.
- Ten patients were treated with either evolocumab or alirocumab for an average of 296 ± 125 days. A statistically significant reduction in total cholesterol (281 ± 52 mg/dl to 197 ± 36 mg/dl; $p = 0.002$) and LDL cholesterol (170 ± 22 mg/dl to 101 ± 39 mg/dl; $p = 0.001$) was observed. No episodes of cardiac rejection, impact on ejection fraction, increased hospitalizations, or increased infections was observed.

Rangaswami J, et al. (2019). Cardiovascular disease in the kidney transplant recipient: epidemiology, diagnosis and management strategies. *Nephrol Dial Transplant*. 34(5), 760-773. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/30984976/>

- Overview of epidemiology, diagnosis and management of cardiovascular diseases (CVD) in kidney transplant recipients
- Highlights major risk factors for CVD, gaps in existing literature, and emphasizes need for multidisciplinary collaboration to reduced CVD after kidney transplant

Whelton PK, et al. (2018). 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 71(19), e127-e248. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/29146535>

- Guidelines published by the AHA and ACC on the management of high blood pressure in adults.
- Includes section specific to renal transplant recipients.

Grundy SM, et al. (2018). 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. *J Am Coll Cardiol*. Retrieved from <https://doi.org/10.1016/j.jacc.2018.11.003>.

- Guidelines published by the ACC and AHA on the treatment of cholesterol to reduce CV risk in adults.

Neuberger JM, et al. (2017). Practical recommendations for long-term management of modifiable risks in kidney and liver transplant recipients: a guidance report and clinical checklist by the Consensus on Managing Modifiable Risk in Transplantation (COMMIT) group. *Transplantation*, 101(4S), S1-S56. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28328734>

- A review of cardiovascular risk after solid organ transplant, donor and recipient risk factors, prevention and treatment strategies, as well as final recommendations on management.

Fearon WF, et al. (2017). Angiotensin-Converting Enzyme Inhibition Early After Heart Transplantation. *J Am Coll Cardiol*. 69(23), 2832-41. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28595700>

- Prospective, multicenter, randomized, double-blind, placebo controlled trial in which 96 heart transplant patients were randomized to receive ramipril or placebo therapy within 8 weeks posttransplant.
- Plaque volumes at 1 year were similar between the ramipril and placebo groups (162.1 ± 70.5 mm³ vs. 177.3 ± 94.3 mm³, respectively; $p = 0.73$). Patients receiving ramipril had improvement in microvascular function as shown by a significant decrease in the index of microcirculatory resistance (IMR) (21.4 ± 14.7 to 14.4 ± 6.3 ; $p = 0.001$) and increase in coronary flow reserve (3.8 ± 1.7 to 4.8 ± 1.5 ; $p = 0.017$), from baseline to 1 year. This did not occur with IMR in the placebo-treated patients.
- Ramipril stabilized the levels of endothelial progenitor cells and improves microvascular function, which has been associated with long term survival after heart transplant.

Greenway SC, et al. (2016). Statin therapy is not associated with improved outcomes after heart transplantation in children and adolescents. *J Heart Lung Transplant*. 35 (4), 457 – 65.

Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/26746989>

- Retrospective review of 964 pediatric (ages 5 to 18 years) heart transplant recipients in the multicenter Pediatric Heart Transplant Study registry from 2001 to 2012. Patients were excluded if they were undergoing re-transplantation, survived <1 year post-transplant, or had missing data regarding statin use. The effects of statins beyond the first year were estimated by Kaplan-Meier and Cox regression multivariable analysis for freedom from PTLD, rejection requiring treatment, any severity of CAV, and survival.
- Statin use was variable among participating centers with only 30% to 35% of patients ≥ 10 years of age started on a statin at <1 year post-transplant. After the first year post-transplant, statin-treated children (average age at transplant 13.24 ± 3.29 years) had significantly earlier rejection (HR 1.42, 95% CI 1.11 to 1.82, $p = 0.006$) compared with untreated children (transplanted at 12 ± 3.64 years) after adjusting for conventional risk factors for rejection. Freedom from PTLD, CAV and overall survival up to 5 years post-transplant were not affected by statin use, although the number of events was small.

Munagala MR and Phanco A. (2016). Managing cardiovascular risk in the post solid organ transplant recipient. *Med Clin North Am.* 100(3), 519-33. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/27095643>

- Overview of major cardiovascular risk factors in solid organ transplant including metabolic syndrome, post-transplant diabetes, hypertension, tobacco use, and obesity.

Eckel RH, et al. (2014). 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 129(25 Suppl 2), S76-99. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/24222015>

- Guidelines published by the AHA and ACC on lifestyle modifications related to diet and physical activity to reduce CV risk in adults.

Palmer SC, et al. (2014). HMG CoA reductase inhibitors (statins) for kidney transplant recipients. *Cochrane Database Syst Rev.* 28(1), CD005019. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/24470059>

- Data was derived from randomized controlled trials and quasi-randomized controlled trials. It was found that statins may reduce major cardiovascular events (1 study, 2102 participants: RR 0.84, CI 0.66 to 1.06), cardiovascular mortality (4 studies, 2322 participants: RR 0.68, CI 0.45 to 1.01), and fatal or non-fatal myocardial infarction (1 study, 2102 participants: RR 0.70, CI 0.48 to 1.01); although effect estimates lack precision and include the possibility of no effect.
- Statins had uncertain effects on all-cause mortality (6 studies, 2760 participants: RR 1.08, CI 0.63 to 1.83); fatal or non-fatal stroke (1 study, 2102 participants: RR 1.18, CI 0.85 to 1.63); creatine kinase elevation (3 studies, 2233 participants: RR 0.86, CI 0.39 to 1.89); liver enzyme elevation (4 studies, 608 participants: RR 0.62, CI 0.33 to 1.19); withdrawal due to adverse events (9 studies, 2810 participants: RR 0.89, CI 0.74 to 1.06); and cancer (1 study, 2094 participants: RR 0.94, CI 0.82 to 1.07).
- Statins significantly reduced serum total cholesterol (12 studies, 3070 participants: MD -42.43 mg/dL, CI -51.22 to -33.65); low-density lipoprotein cholesterol (11 studies, 3004 participants: MD -43.19 mg/dL, CI -52.59 to -33.78); serum triglycerides (11 studies, 3012 participants: MD -27.28 mg/dL, CI 34.29 to -20.27); and lowered high-density lipoprotein cholesterol (11 studies, 3005 participants: MD -5.69 mg/dL, CI -10.35 to -1.03).
- Statins may reduce cardiovascular events in kidney transplant recipients, although treatment effects are imprecise. Statin treatment has uncertain effects on overall mortality, stroke, kidney function, and toxicity outcomes in kidney transplant recipients. Additional studies would improve our confidence in the treatment benefits and harms of statins on cardiovascular events in this clinical setting.

Weiner DE, et al. (2012). Kidney function and risk of cardiovascular disease and mortality in kidney transplant recipients: the FAVORIT trial. *Am J Transplant.* 12(9), 2437-45. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/22594581>

- Post hoc analysis of FAVORIT a multicenter, double-blind, randomized, controlled clinical trial to determine whether lowering homocysteine levels with vitamin therapy reduces the rate of arteriosclerotic CVD outcomes.
- Results: In 3676 participants with complete data, there were 527 CVD events over 3.8 years.
- Each 5 ml/min/1.73 m³ higher eGFR at levels below 45 ml/min/1.73 m³ was associated with a 15% lower risk of both CVD (HR = 0.85) and death (HR = 0.85), while there was no association between eGFR and outcomes at levels above 45 ml/min/1.73 m³.
- Conclusion: In stable kidney transplant recipients, lower eGFR is independently associated with adverse events, suggesting that reduced kidney function itself rather than pre-existing comorbidity may lead to CVD.

Jardine AG, et al. (2011). Prevention of cardiovascular disease in adult recipients of kidney transplants. *Lancet.*, 378(9800), 1419-27. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/22000138>

- A review of conventional cardiovascular risk factors associated with adverse outcomes after kidney transplant.

Watorek E, et al. (2011). Cardiovascular risk in kidney transplant recipients receiving mammalian target of rapamycin inhibitors. *Transplant Proc.* 43(8), 2967-9. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/21996202>

- Studied 115 kidney transplant recipients that were treated with mTOR inhibitor plus steroids compared to a control group of 58 kidney transplant recipients who received calcineurin inhibitor, mycophenolate mofetil or sodium and steroids.
- Results: mTOR inhibitor group showed higher mean levels of total cholesterol (249 vs. 204.6 mg/dL, p<0.0001) and LDL (136.5 vs. 117.7 mg/dL, p=0.015), as well as triglycerides (202 vs. 142 mg/dL; p<0.0001). Mean eGFR was lower in the mTOR inhibitor group vs. control (42.9 vs. 51.9; p=0.0003). Incidence of coronary artery disease was higher among patients treated with mTOR inhibitors than control (p=0.04).
- CVD, defined as MI, PCI, stroke, aortic aneurysm, PE, sudden cardiac death appeared in 26 patients in mTOR inhibitor group vs. 4 patients in control group (p=0.24).
- Conclusions: No real correlation of increased incidence of CVD among the patients on mTOR inhibitor vs. control, although there was a higher burden of cardiovascular risk factors in that group. More studies needed for confirmation.

Israni AK, et al. (2010). PORT investigators. Predicting coronary heart disease after kidney transplantation: Patient Outcomes in Renal Transplantation (PORT) Study. *Am J Transplant.* 10(2), 338-53. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/20415903>

- Retrospective, observational, multi-center study comparing traditional and non-traditional CHD risk factors. Additionally, the PORT investigators developed risk-prediction equations for kidney transplant in standard clinical practice.
- 23,575 kidney transplant patients were included from 14 centers worldwide.
- Results: CHD cumulative incidence was 3.1%, 5.2%, and 7.6% at 1, 3, and 5 years post-transplant, respectively.
- They identified transplant-related risk factors: pre-transplant diabetes, new onset post-transplant diabetes, prior pre- and post-transplant CV events, estimated GFR, delayed graft function, acute rejection, age, sex, race, and duration of pre-transplant ESRD.
- The risk-prediction equations performed well, with the time-dependent c-statistic greater than 0.75.
- Conclusion: transplant-related risk factors, especially those linked to graft function, explain the variation seen in CHD after kidney transplant.

Knight SR, Morris PJ. (2010). Steroid avoidance or withdrawal after renal transplantation increases the risk of acute rejection but decreases cardiovascular risk. A meta-analysis. *Transplantation*, 89(1), 1-14. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/20061913>

- Meta-analysis of randomized controlled trials comparing maintenance steroid group with complete avoidance or withdrawal of steroids.
- 34 studies were analyzed with 5637 patients.
- Results: Steroid avoidance or withdrawal was associated with significantly increased risk of acute rejection over maintenance steroids (RR 1.56, $p < 0.0001$). No significant differences seen among the groups in corticosteroid resistant acute rejection, patient survival, or graft survival. Cardiovascular risk factors including hypertension (RR 0.90, $p < 0.0001$), new onset diabetes (RR 0.64, $p = 0.0006$), and hypercholesterolemia (RR 0.76, $p < 0.0001$) were reduced significantly by steroid avoidance or withdrawal.
- Conclusion: There were significant benefits in cardiovascular risk profiles with steroid avoidance or withdrawal, however with an increase in risk of acute rejection. In addition, there was no difference on graft function, or graft and patient survival between the groups.

Watt KD, Charlton MR. (2010). Metabolic syndrome and liver transplantation: a review and guide to management. *J Hepatol.* 53(1), 199-206. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/20451282>

- A review article on the diagnosis, management, and consequences of obesity, diabetes, dyslipidemia, hypertension post-liver transplant.

Zeier M, van der Giet M. (2010). Calcineurin inhibitor sparing regimens using m-target of rapamycin inhibitors: an opportunity to improve cardiovascular risk following kidney transplantation? *Transpl Int.* 24(1), 30-42. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/20642495>

- A review article of all the pertinent studies involving the conversion of calcineurin inhibitor based maintenance immunosuppression to mTOR inhibitors and the potential to reduce cardiovascular disease following kidney transplantation.

Hillebrand U, et al. (2009). Blood pressure, antihypertensive treatment, and graft survival in kidney transplant patients. *Transpl Int.* 22(11), 1073-80. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/19624495>

- Retrospective analysis of patients who received kidney transplant from 1993-2003 investigating whether long-term graft survival was improved in patients who received long-term ACE-I/ARB or CCB for at least two years.
- Patients were stratified based on their blood pressure one-year after transplant as controlled (<130/80 mmHg) or uncontrolled (>130/80 mmHg) and according to the antihypertensive medication taken (ACE-I/ARB or CCB).
- Results: Graft survival was longer in the controlled group than in the non-controlled group ($p < 0.05$). Graft survival was longer in patients who received long-term treatment with ACE-I/ARB, CCB, or combination of ACE-I/ARB and CCB ($p < 0.001$).
 - The benefits of ACE-I/ARB therapy were more pronounced in the non-controlled group compared to the controlled group.
 - As seen in previous studies, CNI treated kidney transplant recipients benefit from CCB treatment.
- Conclusion: Long-term ACE-I/ARB and CCB therapy is beneficial for graft survival, especially in patients with diabetes and/or albuminuria.

Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. (2009). *Am J Transplant.* 9(Suppl 3), S1-155. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/19845597>

- Specific guidelines on different topics pertaining to kidney transplant with subsequent literature references and treatment options for kidney transplant recipients. Additionally, specific guidelines on monitoring are provided.
- Chapter 16: Hypertension, Dyslipidemias, Tobacco Use, and Obesity
- Chapter 17: Cardiovascular disease management

Pham PT, Pham PC, Danovitch GM. (2007). Cardiovascular disease post-transplant. *Semin Nephrol.* 27(4), 430-44. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/17616275>

- A review of post-transplant complications associated with increased morbidity and mortality after renal transplantation. Also provided are conventional and unconventional cardiovascular risk factors after renal transplant and an approach to their medical management.

Ojo AO. (2006). Cardiovascular complications after renal transplantation and their prevention. *Transplantation.* 82(5), 603-611. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/16969281>

- A review that focuses on both traditional and novel cardiovascular risk factors and also on both primary and secondary preventative strategies that are available for the management of post-transplant CVD in renal transplant patients.
- Risk factors that are mentioned in this review include: hypertension, diabetes mellitus, dyslipidemias, obesity, tobacco use, left ventricular hypertrophy, and anemia.

Holdaas H, et al. (2005). Assessment of Lescol in Renal Transplantation (ALERT) Study Investigators. Long-term cardiac outcomes in renal transplant recipients receiving fluvastatin: the ALERT extension study. *Am J Transplant.* 5(12): 2929-36. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/16303007>

- Randomized, double-blind, placebo-controlled trial of patients receiving cyclosporine based immunosuppression followed for 5-6 years in the primary study. This was an open-label 2-year extension study of fluvastatin 80 mg/day.
 - Dose increased to fluvastatin 40 mg twice daily after two years due to landmark trials indicating a relationship between LDL concentrations and decreasing CV events.
 - Primary endpoint was time to first major adverse cardiac event (MACE) [defined as cardiac death, non-fatal MI, and cardiac intervention procedures].
 - Secondary endpoints included: cardiac death or non-fatal MI, renal graft loss, individual cardiac events, and all-cause mortality.
- Results: Patients randomized to fluvastatin had a reduced risk of MACE (HR 0.79, p=0.036) and a 29% reduction in cardiac death or definite non-fatal MI (HR 0.71, p=0.014). Total mortality and graft loss did not differ between groups.
- Conclusion: Fluvastatin produces a safe and effective reduction in LDL with reduced risk of MACE in kidney transplant recipients.

Jardine AG, et al. (2005). Cardiovascular risk and renal transplantation: post hoc analyses of the Assessment of Lescol in Renal Transplantation (ALERT) Study. *Am J Kidney Dis.* 46(3), 529-36. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/16129216>

- Randomized, double-blind, parallel-group study that compared fluvastatin (Lescol) with placebo followed up for a minimum of 5 years and maximum of 6 years.
- Patients were adult renal transplant recipients who had received a transplant at least 6 months previously and whose graft function was stable. All patients received cyclosporine-based immunosuppression and no patient was administered statins before recruitment.
- Results: Pre-existing coronary heart disease (HR 3.69; p<0.001), total cholesterol level (HR, 1.55 per 50 mg/dL; p=0.0045), and prior acute rejection (HR, 2.36; p=0.0023) were independent risk factors. Independent risk factors for cardiac death were age, diabetes, ST-T changes on the ECG, and serum creatinine level.

Miller LW. (2002). Cardiovascular toxicities of immunosuppressive agents. *Am J Transplant.* 2(9), 807-18. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/12392286>

- A review article that compares the mechanism and intensity by which individual immunosuppressive agents may affect cardiovascular risk factors (hypertension, diabetes, dyslipidemias, etc.) potentially allowing practitioners to design strategies or tailor maintenance immunosuppression for individual patients.

8.3. Post-transplant diabetes mellitus

Lawrence SE, et al. (2023). Sweet and simple as syrup: A review and guidance for use of novel antihyperglycemic agents for post-transplant diabetes mellitus and type 2 diabetes mellitus after kidney transplantation. *Clin Transplant*. Mar;37(3):e14922. Retrieved from:

<https://pubmed.ncbi.nlm.nih.gov/36708369/>

- Review of novel antihyperglycemic agents (SGLTi, GLP1RA, DPP4i) in kidney transplant recipients with type 2 diabetes mellitus or post-transplant diabetes mellitus
- Available literature is primarily single-center retrospective reviews and case series; summarizes available literature and provides recommendations for use of novel antihyperglycemic agents post-transplant

Lin Y, et al. (2023). Use of sodium-glucose co-transporter 2 inhibitors in solid organ transplant recipients with pre-existing type 2 or post-transplantation diabetes mellitus: A systematic review. *Transplant Rev*. Jan;37(1):100729. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/36427372/>

- Systematic review evaluating current safety and efficacy of SGLT2 inhibitors in solid organ transplant recipients with pre-existing type 2 diabetes mellitus or post-transplantation diabetes mellitus
- SGLT2 inhibitors may be an alternative for diabetes management in transplant recipients however close monitoring and patient education should be considered

Newman JD, et al. (2022). Post-transplant diabetes mellitus following heart transplantation. *J Heart Lung Transplant*. Nov;41(11):1537-1546. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35970647/>

- Review of the definition, incidence, risk factors, pathophysiology, clinical outcomes, treatment options, pharmacologic considerations, and future directions in post-transplant diabetes mellitus (PTDM) after heart transplant.
- Available guidelines do not recommend any specific glucose lowering agent and data available is limited, recommendations for treatment are based on expert consensus. The success of the SGLT-2 inhibitors and GLP-1 receptor agonists in the treatment of cardiovascular disease and potential mechanistic benefits has created interest in the ability of these agents to improve outcomes in patients post heart transplant.

Richardson B, et al. (2022). Personalizing Diabetes Management in Liver Transplant Recipients: The New Era for Optimizing Risk Management. *Hepatol Commun*. Jun;6(6):1250-1261. Retrieved from:

<https://pubmed.ncbi.nlm.nih.gov/34921530/>

- Review on the role of the extra-glycemic effects of available anti-diabetes medications and the safety considerations in liver transplant recipients.
- Alternatives to insulin should be strongly considered, when feasible, for personalized long-term management based on risk factors and co-morbidities.

Kotha S, et al. (2021). Impact of immunosuppression on incidence of post-transplant diabetes mellitus in solid organ transplant recipients: Systematic review and meta-analysis. *World J Transplant*. Oct 18;11(10):432-442. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34722172/>

- Meta-analysis that estimated the risk of developing post-transplant diabetes mellitus (PTDM) was higher with tacrolimus (OR = 1.4 95%CI: 1.0–2.0) and sirolimus (OR = 1.8; 95%CI:1.5–2.2) than with Cyclosporine. The overall incidence of PTDM at 2-3 years was 17% for kidney, 19% for liver and 22% for heart. Tacrolimus has higher diabetogenicity 2-3 years post-transplant, whereas sirolimus has higher diabetogenicity 5-10 years post-transplant.

Montada-Atin T, et al. (2021). Recent advances in new-onset diabetes mellitus after kidney transplantation. *Prasad GVR. World J Diabetes*. 15;12(5):541-555. Retrieved from:

<https://pubmed.ncbi.nlm.nih.gov/33995843/>

- Review of the available literature on newer glucose-lowering therapeutics in solid organ transplant, mainly sodium glucose transporter 2 inhibitors, glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase 4 inhibitors, their mechanism of action, benefits, risks, and safety profiles.

Montero N, et al. (2021). Management of post-transplant diabetes mellitus: an opportunity for novel therapeutics. *Clin Kidney J.* 15(1):5-13. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35265335/>

- Review of the published literature on newer antidiabetic agents, including glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and sodium-glucose co-transporter 2 inhibitors, and their use post-kidney transplant including efficacy, safety, and interactions with immunosuppression.

Kim HD, et al. (2021). Effect of everolimus with low-dose tacrolimus on development of new-onset diabetes after transplantation and allograft function in kidney transplantation: A multicenter, open-label, randomized trial. *Ann Transplant.* 26, e927984. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33479188/>

- Multicenter, open-label, randomized, controlled, parallel study that investigated the effect of everolimus with low-dose tacrolimus on the development of post-transplantation diabetes mellitus in kidney transplantation.
- The 1-year cumulative incidence of post-transplantation diabetes mellitus (PTDM) in all patients (n=77) was 7.8%.
- There was no difference in the significant difference in the 1-year cumulative incidence of PTDM between the everolimus (n=38) and tacrolimus (n=39) groups (EVL vs TAC; 13.16% vs 2.56%; P=0.0819).
- There was no significant difference from baseline to 1-year homeostatic model assessment insulin resistance (HOMA-IR) between the EVL and TAC groups (0.03 vs 0.18; P=0.2688)
- The eGFR values at 9 months and 12 months were significantly higher than the value at baseline in the EVL group (9 months, P=0.0242; 12 months, P=0.0491)

Sanyal D, Biswas M, Chaudhari N. (2021). Long-term efficacy and safety of anti-hyperglycaemic agents in new-onset diabetes after transplant: Results from outpatient-based 1-year follow-up and a brief review of treatment options. *Metab Syndr.* 15(1),13-19. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33278690/>

- Retrospective, cross-sectional study evaluating long-term efficacy and safety of anti-hyperglycemic agents in adult living donor kidney transplant recipients newly initiated on anti-hyperglycemic agents for new-onset diabetes after transplantation (NODAT)
- There was a significant decrease in mean FPG, PPG and HbA1c at 1-year from baseline ($p < 0.0001$)

Oikonomaki D, Dounousi E, Duni A, Roumeliotis S, Liakopoulos V. (2021). Incretin based therapies and SGLT-2 inhibitors in kidney transplant recipients with diabetes: A systematic review and meta-analysis. *Diabetes Res Clin Pract.* 172, 108604. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33338553/>

- A systematic review and meta-analysis of efficacy and safety of DPP-4 inhibitors, GLP-1 receptor agonists and SGLT-2 inhibitors in post-transplantation diabetes mellitus
- There was a significant difference between the mean values of HbA1c after and before treatment (random effects model, -0.39; 95% CI, -0.52 to -0.25)
- There was no statistically significant change in the eGFR after administration of DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1 receptor agonists.

Anderson S, Cotiguala L, Tischer S, Park JM, McMurry K. (2021). Review of newer antidiabetic agents for diabetes management in kidney transplant recipients. *Ann Pharmacother.* 55(4), 496-508. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32795145/>

- A systematic review of current literature on the efficacy, safety, drug interactions and timing of initiation of DPP-4 inhibitors, GLP-1 receptor agonists and SGLT-2 inhibitors in kidney transplant recipients

Do V, Haakinson D, Belfort De Aguiar R, Cohen E. (2021). Implementing a pharmacist-led transition of care model for posttransplant hyperglycemia. *Am J Health Syst Pharm*. Online ahead of print. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33821878/>

- Data on the implementation of a pharmacist-managed transition of care program for post-transplant hyperglycemia and decreased incidence of readmission for hyperglycemia

Zielińska K, Kukulski L, Wróbel M, Przybyłowski P, Zakliczyński M, Strojek K. (2020). Prevalence and risk factors of new-onset diabetes after transplantation (NODAT). *Ann Transplant*. 25, e926556. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32839423/>

- Retrospective review on heart transplant patients. Excluded patients with DM at the time of transplant (n=60). Included 276 patients and divided them in 2 groups patients that developed NODAT (n=109) and patients without NODAT (n=167) then performed a logistic regression analysis to assess risk factors for NODAT. Identified the following risk factors for development of NODAT: BMI at discharge and history of diagnosed CMV, and age over 51 as independent risk factors.

Lo C, et al. (2020). Glucose-lowering agents for treating pre-existing and new-onset diabetes in kidney transplant recipients. *Cochrane Database Syst Rev*.8, CD009966. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32803882/>

- Meta-analysis of newer agents for NODAT in kidney transplant recipients (KTR).
- Included 10 different RCTs, quasi-RCTs and cross-over studies evaluating these newer agents. There were no studies fitting the criteria that examined the effects of biguanides, glinides, GLP-1 agonist, or sulfonylureas.
- Evidence examining these agents in kidney transplant recipients is mostly of low to very low certainty. There is a need for larger, blinded, high-quality RCTs to evaluate and compare safety and efficacy of different glucose-lowering agents in KTR.

Tsai SF, Chen CH. (2019). Management of diabetes mellitus in normal renal function, renal dysfunction and renal transplant recipients, focusing on glucagon-like peptide-1 agonist: A review based upon current evidence. *Int J Mol Sci*. 20(13), 3152. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6651241/>

- Review on GLP-1 agonist use in KTR. Though evidence is limited, this review includes an overview of studies examining the transplant specific pharmacokinetic and pharmacodynamic effects of GLP-1 use.
- Concluded GLP-1 agonist may target pathogenesis of NODAT and are a viable option for glycemic control in KTR. Given delayed gastric emptying caused by GLP-1 agonists, the authors of this study endorse an influence of immunosuppressant concentrations and recommend close monitoring.

Sparks JD, et al. (2019). New-onset diabetes after pediatric heart transplantation: A review of the Pediatric Heart Transplant Study. *Pediatr Transplant*. 23(5), e13476. Retrieved from:

<https://pubmed.ncbi.nlm.nih.gov/31124221/>

- Retrospective, multicenter evaluation of all pediatric heart transplant recipients from 2004 to 2014. Compared and evaluated NODAT incidence, associated factors, and outcome analysis at 1-year post-transplant.
- Black (non-Hispanic) patients (p=0.002), older at time of transplant (p<0.0001), and higher BMI percentile at the time of transplant (p<0.0001) were more likely to have NODAT.
- The overall incidence of NODAT in this pediatric population remained low, ranging from 1.1% to 7.4% in a 10-year follow up period.

Dedinska I, et al. (2018). The role of proteinuria, paricalcitol and vitamin D in the development of posttransplant diabetes mellitus. *Bratisl Lek Listy*. 119(7), 401-407. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pubmed/?term=30160127>

- This study in 167 kidney transplant recipients identified vitamin D deficiency, proteinuria, and hyperphosphatemia as independent risk factors for NODAT. Paricalcitol was identified as a protective factor for NODAT.

Bzoma B, et al. (2018). New-onset diabetes mellitus after kidney transplantation-a paired kidney analysis. *Transplant Proc.* 50(6), 1781-1785. Retrieved from:

<https://www.sciencedirect.com/science/article/pii/S0041134518303063?via%3Dihub>

- This retrospective study determined acute rejection, older age, higher Charlson Comorbidity Index, and BMI as independent risk factors for NODAT in kidney transplant recipients.

Cehic MG, et al. (2018). Management strategies for post-transplant diabetes mellitus after heart transplantation: a review. *Journal of Transplantation*, 2018, 1025893. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5829348/>

- This is a review of PTDM and current management strategies, including a review of newer classes of treatment such as SGLT2 inhibitors, GLP1 agonists and DPP-4 inhibitors

Mourad G, et al. (2017). Incidence of posttransplantation diabetes mellitus in de novo kidney transplant recipients receiving prolonged release tacrolimus-based immunosuppression with 2 different corticosteroid minimization strategies: ADVANCE, A randomized controlled trial. *Transplantation*, 101(8),1924. Retrieved from: <https://insights.ovid.com/pubmed?pmid=27547871>

- ADVANCE (NCT01304836) was a phase 4, multicenter, prospectively randomized, open-label, 24-week study comparing the incidence of post-transplantation diabetes mellitus (PTDM) with 2 prolonged-release tacrolimus corticosteroid minimization regimens
- The full-analysis set included 1081 patients (arm 1: n = 528, arm 2: n = 553)
- Week 24 Kaplan-Meier estimates of PTDM were similar for arm 1 versus arm 2 (17.4% vs 16.6%; P = 0.579).
- Incidence of composite efficacy failure, graft and patient survival, and mean estimated glomerular filtration rate were also comparable between arms.
- Biopsy-proven acute rejection and acute rejection were significantly higher in arm 2 versus arm 1 (13.6% vs 8.7%, P = 0.006 and 25.9% vs 18.2%, P = 0.001, respectively).
- Tolerability profiles were comparable between arms

Banson KA, Maxwell AP, McKnight AJ. (2016). A HuGE Review and Meta-Analyses of Genetic Associations in New Onset Diabetes after Kidney Transplantation. *PLoS One*, 11(1):e0147323. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/26789123>

- Evaluating cumulative evidence for SNPs associated with NODAT in kidney transplant recipients has revealed three SNPs associated with NODAT. An adequately powered, dense genome-wide association study will provide more information using a carefully defined NODAT phenotype.

Vanhove T, Remijsen Q, Kupers D, Gillard P. (2016). Drug-drug interactions between immunosuppressants and antidiabetic drugs in the treatment of post-transplant diabetes mellitus. *Transplant Rev (Orlando)*, pii: S0955470X(16)30078-7. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pubmed/27665059>

<https://www.ncbi.nlm.nih.gov/pubmed/27665059>

Li Z, et al (2016). New-onset diabetes mellitus in liver transplant recipients with hepatitis C: Analysis of the national database. *Transplant Proc.* 48(1):138-44. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pubmed/26915859>

- This study demonstrated that liver transplant recipients with hepatitis C virus have a higher incidence and more risk factors for NODAT compared with non-HCV recipients.

Shivaswamy V, Boerner B, Larsen J. (2016). Post-transplant diabetes mellitus: Causes, treatment, and impact on outcomes. *Endocr Rev.* 37(1),37-61. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pubmed/26650437>

- This review discusses the diagnosis of NODAT based on latest consensus guidelines, contributing factors, and how various screening practices and guidelines affect our knowledge of the epidemiology.

Hornum M, et al. (2016). Diagnosis, management and treatment of glucometabolic disorders emerging after kidney transplantation: a position statement from the Nordic Transplantation Societies. *Transplant International*, 26,1049-1060. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/23634804>

- Review of diabetes after transplant, modifiable and non-modifiable risk factors, and treatment options.

Zeltzer SM, Taylor DO, Tang WH. (2015). Long-term dietary habits and interventions in solid-organ transplantation. *J Heart Lung Transplant*. 34(11),1357-65. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/26250965>

- Review of the literature related to dietary interventions and post-transplant metabolic complications, including dyslipidemia, diabetes, and obesity.

Sharif A, et al. (2014). New onset diabetes after transplantation guidelines: Proceedings from an international consensus meeting on post-transplantation diabetes mellitus: Recommendations and future directions; *Am J Transplant*. 14(9), 1992-2000. Retrieved from: <https://onlinelibrary.wiley.com/doi/full/10.1111/ajt.12850>

- Recommendations include: terminology revision from new-onset diabetes after transplantation to posttransplantation diabetes mellitus (PTDM), exclusion of transient post-transplant hyperglycemia from PTDM diagnosis, expansion of screening strategies (incorporating postprandial glucose and HbA1c) and opinion-based guidance regarding pharmacological therapy in light of recent clinical evidence.

J. Ekberg, H. Ekberg, P.Lindner. (2014). An in-progress, open-label, multi-centre study (SAILOR) evaluating whether a steroid-free immunosuppressive protocol, based on ATG induction and a low tacrolimus dose, reduces the incidence of new onset diabetes after transplantation; *Transplant Res*. 3, 12. Retrieved from: <https://transplantationresearch.biomedcentral.com/articles/10.1186/2047-1440-3-12>

- Prospective, multi-centre, controlled, randomized, parallel group, open-label study involving kidney transplant patients, comparing a steroid-free immunosuppressive protocol (low-dose tacrolimus and MMF with ATG induction) with low-dose tacrolimus, MMF and steroids with anti IL2-R induction.
- The primary objective of the study is to assess the cumulative incidence of NODAT in the two study arms 12 months after transplantation using the American Diabetes Association type 2 diabetes diagnostic criteria

Therasse A, et al. (2013). Management of Post-Transplant Diabetes. *Current Diabetes Reports*, 13, 121-29. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/23188594>

- Review article discussing management of post-transplant diabetes.

Ghisdal L, et al. (2012). New Onset Diabetes After Renal Transplantation. *Diabetes Care*, 35: 181-88. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/22187441>

- Review article highlighting the risk factors for NODAT as well as management of care

Pham PT, et al. (2011). New onset diabetes after transplantation (NODAT): an overview. *Diabetes Metab Syndr Obesity*. 2011, 4:175-186. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/21760734>

- A review article on NODAT including diagnostic criteria, incidence after solid organ transplant, suggested risk factors and potential mechanisms as well as management.

Lane, JT et al (2011) Approach to the Patient with New Onset Diabetes after Transplantation (NODAT). *J Clin Endocrinol Metab*, 96(11):3289-3297. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/22058376>

- Review article explaining suggested approaches to treating patients with new onset diabetes.

Kuo, HT et al. (2010). Associations of pretransplant diabetes Mellitus, new-onset diabetes after transplant, and acute rejection with transplant Outcomes: An analysis of the Organ Procurement and Transplant Network/United Network for Organ Sharing (OPTN/UNOS) Database. *Am J Kidney Dis*. 56,1127-1139. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/20934793>

- Pre-existing diabetes is a major concern in renal transplant patients. It can serve as a predictor for mortality and rejection during the first year.

Vincenti F, et al. (2007). Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. *Am J Transplant.* 7(6), 1506-14.

Retrieved from: <https://onlinelibrary.wiley.com/doi/full/10.1111/j.1600-6143.2007.01749.x>

- DIRECT (Diabetes Incidence after Renal Transplantation: Neoral C(2) Monitoring Versus Tacrolimus) was a 6-month, open-label, randomized, multicenter study which used American Diabetes Association/World Health Organization criteria to define glucose abnormalities. De novo renal transplant patients were randomized to cyclosporine microemulsion (CsA-ME, using C(2) monitoring) or tacrolimus, with mycophenolic acid, steroids and basiliximab. The intent-to-treat population comprised 682 patients (336 CsA-ME, 346 tacrolimus)
- Results: NODAT or impaired fasting glucose (IFG) at 6 months, occurred in 73 CsA-ME patients (26.0%) and 96 tacrolimus patients (33.6%, $p = 0.046$). BPAR, graft loss or death at 6 months, occurred in 43 CsA-ME patients (12.8%) and 34 tacrolimus patients (9.8%, $p = 0.211$). Mean glomerular filtration rate (Cockcroft-Gault) was 63.6 ± 20.7 mL/min/1.73 m² in the CsA-ME cohort and 65.9 ± 23.1 mL/min/1.73 m² with tacrolimus ($p = 0.285$); mean serum creatinine was 139 ± 58 and 133 ± 57 mmol/L, respectively ($p = 0.005$). Blood pressure was similar between treatment groups at month 6, but total cholesterol, LDL-cholesterol and triglyceride levels were significantly higher with CsA than with tacrolimus (total cholesterol:HDL remained unchanged).
- The profile and incidence of adverse events were similar between treatments.

Shah T, et al (2006) Risk Factors for development of new-onset diabetes mellitus after kidney transplantation. *Transplantation*,82,1673-1676. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/17198258>

- Study done using the OPTN/UNOS database to identify risk factors associated with the development of NODAT.

Wilkinson A, et al. (2005). Guidelines for the treatment and management of new-onset diabetes after transplantation. *Clin Transplant.* 2005,19(3):291-8. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pubmed/15877787>

- New onset diabetes after transplantation guidelines.

Davidson, J et al. (2003). New-onset diabetes after Transplantation: 2003 International Consensus Guidelines. *Transplantation*, 75 (10), SS3-SS24. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/12775942>

- New onset diabetes after transplantation guidelines.

8.4. Biliary complications and management

Matusushima H, et al. (2023). Biliary Complications Following Split Liver Transplantation in Adult Recipients: A Matched Pair Analysis on Single-Center Experience. *Liver Transplantation.* Mar 1;29(3):279-289. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/36811877/>

- Retrospective study of adult liver deceased donor liver transplant recipients assessing incidence of biliary complications in those receiving split liver versus whole liver transplantation
- Graft and survival rates were similar between split liver and whole liver transplantation but split liver transplantation increases the risk of biliary leakage compared to whole liver transplantation

Suo L, et al. (2023). Risk Factors Related to Early Biliary Complications After Liver Transplantation: A Single-Center Analysis. *Transplant Proc.* Jan-Feb; 55(1):164-169. Retrieved from:

<https://pubmed.ncbi.nlm.nih.gov/36707363/>

- Retrospective study of liver transplant recipients evaluating the risk factors for early biliary complications and effective treatments
- Warm ischemia time and operative time were independent risk factors associated with development of early biliary complications. Endoscopic retrograde cholangiopancreatography was safe in the management of early biliary complications.

Georges P, et al. (2022). Post-Transplantation Cytomegalovirus Infection Interplays with the Development of Anastomotic Biliary Strictures After Liver Transplantation. *Transpl Int.* 35:10292. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35721468/>

- Retrospective study with the aim to identify new postoperative risk factors for anastomotic biliary stricture. On multivariable analysis, donor BMI, post-liver transplant CMV infection and the occurrence of post-liver transplant anastomotic biliary fistula were associated with anastomotic biliary stricture. Anastomotic technical difficulty did not independently impact the risk. The occurrence of anastomotic biliary stricture was not associated with overall patient survival or graft survival.

Matar AJ, et al. (2021). Biliary Complications Following Adult Deceased Donor Liver Transplantation: Risk Factors and Implications at a High-volume US Center. *Transplant Direct.* 7(10):e754. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34514109/>

- Retrospective single center review of 647 deceased donor liver transplant (DDLT) recipients from a donor after brain death (DBD) between examining the pretransplant and intraoperative risk factors associated with biliary complications at a high-volume tertiary care center and determine the impact of these complications on the posttransplant course and long-term transplant outcomes.
Risk factors for biliary leak included recipient age and cold ischemic time, whereas alcoholic cirrhosis as transplant indication was a risk factor for biliary stricture. Placement of a biliary stent was associated with the development of both biliary leaks and anastomotic strictures. While posttransplant, biliary leaks were a significant risk factor for future episodes of acute rejection the occurrence did not impact overall survival. However, biliary strictures were associated with a significantly reduced overall survival at 1- and 4-years post-transplant.

Ly M, Crawford M, Verran D. (2021). Biliary complications in donation after circulatory death liver transplantation: the Australian National Liver Transplantation Unit's experience. *ANZ J Surg.* 91(3), 445-450. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32985774/>

- A retrospective analysis of adult donation after circulatory death (DCD) liver transplant recipients at the Australian National Liver Transplantation Unit
- Biliary complications occurred in 35% of DCD transplant recipients
- Risk factors that were associated with biliary complications included higher donor risk index scores, post-transplant portal vein complications and peak gamma-glutamyl transferase levels within 7 days post-transplant

Li X, Peng J, Ouyang R, Yang Y, Yu C, Lin H. (2021). Risk factors for recurrent primary biliary cirrhosis after liver transplantation: A systematic review and meta-analysis. *Dig Liver Dis.* 53(3), 309-317. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33380381/>

- A systematic review and meta-analysis evaluating the risk factors for primary biliary cirrhosis in liver transplant recipients
- 6 studies of 3,184 patients
- The use of tacrolimus (HR, 2.62; 95% CI, 1.35 to 5.09) was associated with an increased risk of primary biliary cirrhosis recurrence and preventive ursodeoxycholic acid (HR, 0.40; 95% CI, 0.28 to 0.57) was associated with a decreased risk

Kohli DR, Desai MV, Kennedy KF, Pandya P, Sharma P. (2020). Patients with post-transplant biliary strictures have significantly higher rates of liver transplant failure and rejection: a nationwide inpatient analysis. *J Gastroenterol Hepatol.* 10.1111/jgh.15388. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33373488/>

- Retrospective study using the nationwide readmission database (NRD) to assess impact of post-transplant biliary strictures on inpatient mortality, 30-day readmission, transplant rejection/infection/failure and disposition. The study found post-transplant biliary strictures were associated with increased incidence of rejection, allograft failure and infection, and readmissions.

Sneiders D, et al. (2018). Systematic review and meta-analysis of posttransplant hepatic artery and biliary complications in patients treated with transarterial chemoembolization before liver transplantation. *Transplantation*. 102(1), :88-96. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28885493>

- Retrospective review of hepatocellular carcinoma patients who received TACE before liver transplantation. The study found that these patients had increased risk of hepatic artery complications, but similar rates of biliary complications.

Dulaney DT, et al. (2017). Tobacco use is a modifiable risk factor for post-transplant biliary complications. *J Gastrointest Surg*. 21(10), 1643-1649. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28785937>

- Retrospective study comparing ever smokers and never smokers and overall biliary complication rate. Biliary complications included strictures, leaks, or bilomas requiring intervention. Positive smoking history at time of transplant was a predictor of biliary complication, while increased time from quit date to transplant was a protective factor.

Radunz S, et al. (2017). Hepatic artery and biliary complications in liver transplant recipients with radioembolization bridging treatment for hepatocellular carcinoma. *Clin Transplant*. 31(11). Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28836737>.

- Radioembolization for hepatocellular carcinoma pre-transplant was associated with decreased odds of biliary complications post-transplant with no statistically significant difference in hepatic artery complications.

Mejia GA, et al. (2016). Biliary complications after liver transplantation: incidence, risk factors and impact on patient and graft survival. *Transplant Proc*. 48(2), 665-8. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/27110025>

- This study included liver transplant patients between 2005 and 2013 at a single center. Of the total population, 17.8% developed biliary complications, with the majority being biliary stenosis. There was no statistically significant difference in patient or graft survival. Patient at higher risk of complications included those with AB blood type, viral hepatitis and alcoholic cirrhosis.

Memeo R, et al. (2015). Management of biliary complications after liver transplantation. *World J Hepatol*. 7 (29), 2890 – 5. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/26689137>

- This article is a review of the treatment of biliary complications after liver transplant.

Shi R, et al. (2015). Gallstones in liver transplant recipients: A single-center study in China. *Turk J Gastroenterol*. 26(5), 429-34. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/26350690>

- This study identified older age and lower Child score as independent risk factors for prevalence of gallstones among liver transplant recipients

Arain, MA, et al. (2013). Advances in endoscopic management of biliary tract complications after liver transplantation. *Liver Transpl*, 19, 482-98. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/23417867>

- Review of endoscopic options for diagnosis and management of biliary complications, including comparison of MRCP and ERCP and discussion of newer accessory devices.

Enestvedt, CK, et al. (2013). Biliary complications adversely affect patient and graft survival after liver retransplantation. *Liver Transpl*, 19, 965-72. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/23818332>

- Graft and patient survival were significantly reduced in liver retransplant patients who had biliary complications, compared to those without biliary complications.

Kocchar, G, et al. (2013). Biliary complications following liver transplantation. *World J Gastroenterol*, 19, 2841-6. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/23704818>

- Review of biliary complications including etiology and management.

Paik, WH, et al. (2013). Long-term clinical outcomes of biliary cast syndrome in liver transplant recipients. *Liver Transpl*, 19, 275-82. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/23213039>

- Single center retrospective analysis of long-term clinical outcomes of patients with biliary cast syndrome post-liver transplant. Acute cellular rejection was noted to be a risk factor for repeated biliary cast development.

Seehofer, D, et al. (2013). Biliary complications after liver transplantation: old problems and new challenges. *Am J Transplant*, 13, 253-65. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/23331505>

- Comprehensive review of biliary complications post-liver transplant, including etiology, diagnosis and interventions.

Voigtlander, T, et al. (2013). Biliary cast syndrome post-liver transplantation: risk factors and outcome. *Liver Int*, 33, 1287-92. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/23601581>

- Single center retrospective analysis of etiology, risk factors, management, and outcomes of patients biliary cast syndrome post-liver transplant. Hepatic artery stenosis, biliary strictures and renal replacement therapy were identified as risk factors.

Zimmerman, MA, et al. (2013). Development, management, and resolution of biliary complications after living and deceased donor liver transplantation: a report from the adult-to-adult living donor liver transplantation cohort study consortium. *Liver Transpl*, 19, 259-67. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/23495079>

- Comparison of incidence of biliary complications in living and deceased donor liver transplant.
- Complications are more common in living donor liver transplantation, but management is similar.

Sharma, S, et al. (2008). Biliary strictures following liver transplantation: past, present and preventive strategies. *Liver Transpl*, 14, 759-69. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/18508368>

- Review of management of biliary strictures post-liver transplant, with a focus on endoscopic and surgical techniques.

Inomata, Y, et al. (2001). Pathogenesis and treatment of bile duct loss after liver transplantation. *J Hepatobiliary Pancreat Surg*, 8, 316-22. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/11521176>

- Report on the management of post-liver transplant bile duct loss from a single center. Bile duct loss was associated with chronic allograft rejection.

Hoffman, RM, et al. (1995). Hepatitis C virus infection as a possible risk factor for ductopenic rejection (vanishing bile duct syndrome) after liver transplantation. *Transpl Int*, 8, 353-9. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/7576016>

- Single center, retrospective review of patients with ductopenic rejection (DR) to identify risk factors. Incidence of hepatitis C infection was significantly higher in patients with DR than in those without DR.

8.5. Calcineurin inhibitor neurotoxicity

Aparicio EV, et al. (2023). Posterior reversible encephalopathy syndrome (PRES) in post liver transplantation. *Rev Esp Enferm Dig*. 115(3), 138-140. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35469414/>

- A case report of MRI-confirmed PRES associated with tacrolimus in a liver transplant patient.

Kemna, MS, et al. (2022). Posterior reversible encephalopathy syndrome (PRES) after pediatric heart transplantation: A multi-institutional cohort. *J Heart Lung Transplant*. Retrieved from: [https://www.jhltonline.org/article/S1053-2498\(22\)02138-6/fulltext](https://www.jhltonline.org/article/S1053-2498(22)02138-6/fulltext)

- Fourteen-center retrospective study of 42 PRES-cases and 1,502 heart transplant-recipients without PRES. PRES occurred in 3.2% of HTx-recipients > 1 year of age; no infants developed PRES. Calcineurin inhibitor (CNI) levels were suprathereapeutic in only 8/42, and CNI-management did not significantly impact outcome. Risk of PRES was 12.8x higher in those with pre-transplant Glenn/Fontan (CI 1.69, 96.27; p = .013) compared to recipients with congenital heart disease without Glenn/Fontan, while sex, age, BMI or ischemic time did not contribute significantly.

Yavuz G, et al. (2022). Posterior reversible encephalopathy syndrome after lung transplantation: Risk factors and management. *Clin Transplant*. e14850. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/36398875/>

- Retrospective review of 30 lung transplant patients with neurological symptoms typical of posterior reversible encephalopathy (PRES). The characteristics of patients who were diagnosed with PRES (n=11) to those who were not (n=19) were compared. The incidence of PRES after lung transplantation was 2%. The risk of developing PRES was significantly associated with age (OR= 0.92, p<0.0001) and having cystic fibrosis (OP=10.1, p<0.0001). Creatinine level and tacrolimus trough level within one week prior to neurological symptoms were significantly higher in patients with PRES.

Ueno T, et al. (2022). Long-Term Outcome After Tacrolimus-Related Neurotoxicity in Pediatric Living Donor Liver Transplantation. *Transplant Proc*. 54(2):468-471. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35074159/>

- Single center retrospective review of 128 pediatric patients who underwent living donor liver transplant between 2007 and 2020 and developed neurologic symptoms with tacrolimus. Tacrolimus-related encephalopathy was observed in 5% of patients. The mean tacrolimus level at encephalopathy was 11 ng/dL. All patients resumed tacrolimus a median of 8 months from onset. No neurologic complications were observed after resuming tacrolimus.

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

- Tacrolimus has a spectrum of neurotoxicities supported by the three distinct profiles: neuro-encephalopathies, axonal polyneuropathies and symptomatic changes in neurological state.
- Presentations of encephalopathies occurred with tacrolimus troughs both within and outside of therapeutic range. Comparatively, as seen with the literature in renal and liver transplant recipients, symptomatic changes in neurological state, such as tremor and changes in mental status, were typically associated with suprathereapeutic tacrolimus levels.
- The discrepancies and ambiguity in these study findings are in agreement with other solid organ transplant studies, highlighting that there is no clear, simple dose-response correlation between tacrolimus and neurotoxicity.

Udomkarnjananun S, et al. (2018). An unusual manifestation of calcineurin inhibitor-induced pain syndrome in kidney transplantation: A case report and literature review. *Am J Case Rep*. 19, 442-446. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/29654227/>

- Calcineurin inhibitor induced pain syndrome (CIPS) is a rare adverse effect that includes debilitating, symmetric bilateral pain in the lower extremities, primarily the feet, ankles, and knees.
- Case report of an unusual presentation of CIPS involving elevated tacrolimus trough of 28.2 ng/mL, severe back pain, and marrow edema on MRI in a kidney transplant recipient that was unresponsive to nifedipine but resolved upon pregabalin use and decrease in tacrolimus concentration.
- A review of studies in MEDLINE from 1966-2017 revealed 7 cohorts of 60 kidney transplant recipients with CIPS. Onset was within 6 months after calcineurin inhibitor (CNI) initiation and was reported most often with trough concentrations in normal range. Radiographic findings included increased radiotracer uptake in affected bones/joints and marrow edema on MRI. Treatments included reduction or withdrawal of CNI, switch to alternate CNI, and/or calcium channel blockers.

Pflugrad H, et al. (2018). Longterm calcineurin inhibitor therapy and brain function in patients after liver transplantation. *Liver Transpl.* 2018;24(1):56-66. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/29156491>

- This study analyzed 85 OLT patients at 10-years post-transplant using cerebral MRIs and psychometric testing. Patients receiving CNI showed significantly worse visuospatial/constructional ability compared with controls ($P \leq 0.04$). Patients on low-dose CNI therapy had overall impaired cognitive function compared with controls ($p=0.01$). Total tacrolimus dose and mean trough level were negatively correlated to cognitive function. Lastly, patients treated with CNI therapy had more white matter hyperintensities than patients on CNI-free therapy ($p < 0.05$). These effects were seen especially in patients already experiencing nephrotoxic side effects.

Gmitterová K, Minár M, Žigrai M, Košutzká Z, Kušnířová A, Valkovič P. (2018). Tacrolimus-induced parkinsonism in a patient after liver transplantation - case report. *BMC Neurol.* 18(1), 44. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/29678162>

- Case report of a 51 year old woman post OLT who developed signs of Parkinsonism with progressive worsening neuropsychiatric symptoms associated with tremors

Alagoz S, Gulcicek S, Oruc M, Trabulus S, Seyahi N. (2016). Gangliocytoma presenting with tacrolimus neurotoxicity in a renal transplant recipient: Case report. *Transplant Proc.* 48(9), 3142-3144. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/27932167>

- Case report of a 21 year old woman post living donor kidney transplant from her mother
- Patient developed neurological deficits within the 1st day of tacrolimus initiation and had a gangliocytoma which could possibly cause CNI-induced neurotoxicity in the early postoperative period

Langone A, et al. (2015). Switching Study of Kidney TRansplant PATients with Tremor to LCP-TacrO (STRATO): an open-label, multicenter, prospective phase 3b study. *Clinical Transplantation.* 29(9), 796–805. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/26113208/>

- Two-sequence, open-label, multicenter, prospective phase IIIb exploratory study of kidney transplant recipients with new onset tremor after transplant on stable doses of immediate-release tacrolimus (IR-Tacro). Subjects were converted to once-daily, extended-release tacrolimus (LCP-Tacro) after 7 days.
- Subjects were evaluated 2 hours after tacrolimus administration by blinded neurologists. The primary efficacy endpoint was mean absolute change in the Fahn-Tolosa-Marin (FTM) tremor rating scale from time of conversion (day 7) to seven days after LCP-Tacro conversion (day 14). Adverse events were also assessed at days 1, 7, 14, and 30.
- There was a significant improvement in absolute FTM score 7 days after subjects were converted to LCP-Tacro (-5.35 , $p < 0.0001$) and percent change in FTM score (-15.59% , $p = 0.005$). There was also significant improvement in Quality of Life in Essential Tremor scale, driven by physical, psychosocial, and work/finance quality of life. Tacrolimus trough levels were similar on days 1, 7, and 14. Incidence of drug-related adverse events were similar between groups (4.5% IR-TAC vs 2.4% LCP-Tacro).

Hayes, D Jr et al. (2013). Alternative Tacrolimus and Sirolimus Regimen Associated With Rapid Resolution of Posterior Reversible Encephalopathy Syndrome After Lung Transplantation. *Pediatr Neurol.* 2014;50(3):272-5. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/24405697>

- Case report of bilateral lung transplant recipient that developed posterior reversible encephalopathy syndrome 6 months post-transplant. She was successfully managed by reducing tacrolimus exposure through use of an alternative regimen of sirolimus combined with reduced-dose tacrolimus.
- Titrated the tacrolimus and sirolimus dose for a combined goal level of 10-20 ng/mL (adding tacrolimus and sirolimus levels together)

Anghel, D et al. (2013). Neurotoxicity of Immunosuppressive Therapies in Organ Transplantation. *Maedica*, 8(2), 170-175. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/24371481>

- Review of mechanisms and manifestations of CNI-induced neurotoxicity.

Kwun, WH. (2011). Tacrolimus related neurologic complication after pediatric kidney transplantation. *J Korean Surg Soc*, 81(3), 225-8. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/22066126>

- Case report of a pediatric renal transplant patient (11 year old girl) who experienced tacrolimus-induced neurotoxicity on post-operative day 12.
- Tacrolimus level was measured at 19.7 ng/mL at the time of symptom appearance. The patient was initially managed with tacrolimus dose adjustments to target a level of 5-10 ng/mL. Full reversal of symptoms was achieved when tacrolimus was changed to cyclosporine.

Furukawr, M, et al. (2001). MRI in seven cases of tacrolimus (FK-506) encephalopathy: utility of FLAIR and diffusionweighted imaging. *Neuroradiology*, 43, 615-621. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/11548166>

- Retrospective analysis of 7 patients with presumed tacrolimus-induced encephalopathy (N= 4 post-liver transplant, N=3 bone marrow transplant). FLAIR was specified as the optimal MRI sequence over DWI to recognize tacrolimus encephalopathy. It was also noted that 5 of 6 patients with clinical data available had sudden electrolyte or fluid changes prior to onset of CNS disturbances.

8.6. Chronic allograft nephropathy/interstitial fibrosis and tubular atrophy

Yamamoto I, et al. (2023). Challenges posed by the Banff classification: diagnosis and treatment of chronic active T-cell mediated rejection. *Nephron*, DOI: 10.1159/000530158. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/36928337/>

- Overview of the 2019 changes in Banff classification and treatment of T-cell mediated rejection (TCMR).

Mohammad, D, et al. (2022). Treatment of BK virus with a stepwise immunosuppression reduction and intravenous immunoglobulin in pediatric kidney transplant. *Pediatric transplantation*, 26(4), e14241. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35122460/>

- Retrospective study of pediatric kidney transplants evaluating the prevalence of BK virus (BKV), BK virus nephropathy (BKVN), treatment outcomes with stepwise immunosuppression reduction (IR), and IVIG. Of the 56 patients included, 35.7% had BKV. Two patients had confirmed, and two had presumed BKVN. The first-line treatment was IR in 100% of patients. Second-line treatment for BKVN confirmed and presumed was IVIG every month for six doses. Viral resolution was achieved in 70%, and no difference was noted in estimated glomerular filtration rate between BKV and non-BKV group.

Lai, X, et al. (2021). Tackling Chronic Kidney Transplant Rejection: Challenges and Promises. *Frontiers in immunology*, 12, 661643. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34093552/>

- Overview of current understanding of pathogenesis, standard diagnosis and challenges in the context of chronic kidney transplant rejection
- Review of recent developments of new biomarkers associated with chronic renal injury and novel therapeutic strategies, which may be promising for improvement of long-term graft and patient survival.

Anandh U, et al. (2021). Kidney transplant dysfunction in a patient with COVID – 19 infection: role of concurrent Sars-Cov 2 nephropathy, chronic rejection and vitamin C-mediated hyperoxalosis: case report. *BMC Nephrol*. 22, 91. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33722190/>

- Case report of a renal allograft recipient with COVID-19 infection who was found to have antibody-mediated rejection, SARS CoV-2 nephropathy and oxalate nephropathy secondary to high-dose vitamin C supplementation

McCaffrey J, Bhute VJ, Shenoy M. (2021). BK virus infection and outcome following kidney transplantation in childhood. *Sci Rep.* 11,2468. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33510329/>

- Retrospective, single-center analysis of 106 pediatric kidney transplant recipients evaluating the incidence, morbidity and risk factors of BK virus and BK virus-associated nephropathy (BKN).
- The incidence of BKN was 7/106 (6.6%) and the median time of BKN development post-transplant was 90.0 days.
- Development of BKN was associated with younger age at transplantation ($p=0.013$) while development of BK viremia was associated with negative recipient serology for CMV at time of transplantation ($p=0.012$) and a higher net level of immunosuppression ($p=0.039$).

Benotmane I, et al. (2021). Intravenous immunoglobulin as a preventive strategy against BK virus viremia and BKV-associated nephropathy in kidney transplant recipients—Results from a proof-of-concept study. *Am J Transplant.* 21,329-37. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32741096/>

- Retrospective, single-center analysis of 174 kidney transplant recipients evaluating whether early IVIG administration prevents BK virus replication in patients with low NAb titers.
- The incidence of BKV viremia was similar between patients with low Nab titers treated with IVIG and those with high Nab titers who did not receive IVIG (6.8% vs 10.1%)
- The incidence of BKV viremia was significantly lower in patients with low Nab titers treated with IVIG compared to untreated patients with low Nab titers (6.8% vs 36.6%; $P<0.001$).
- The median peak viral load was significantly lower in patients with low Nab titers treated with IVIG compared to untreated patients with high Nab titers (4.16 log copies/mL vs 4.97 log copies/mL; $P=0.025$).
- The incidence of BKV-associated nephropathy in patients with low Nab titers treated with IVIG (4.5%) was similar to that observed in untreated patients with high Nab titers (2.2%) and markedly lower than that of the untreated patients with low Nab titers (19.5%; $P = .001$).

The 3C Study Collaborative Group. (2018). Campath, calcineurin inhibitor reduction, and chronic allograft nephropathy (the 3C Study) - results of a randomized controlled clinical trial. *Am J Transplant.* 18(6),1424-1434. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/29226570>

- This RCT included sequential randomizations between alemtuzumab and basiliximab induction, and between tacrolimus and sirolimus maintenance therapy at 6 months post-kidney transplant. Allocation to sirolimus had no significant effect on GFR at 18 months. Biopsy-proven acute rejection and serious infections (opportunistic infections or requiring hospitalizations) were significantly more common among patients in the sirolimus group.
 - Only half of the sirolimus group were taking their medication at 18 months after randomization

Haas M, et al. (2018). The Banff 2017 Kidney Meeting Report: Revised diagnostic criteria for chronic active T cell-mediated rejection, antibody-mediated rejection, and prospects for integrative endpoints for next-generation clinical trials; *Am J Transplant.* 18(2),293. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/29243394>

- Updates from the 2017 Banff Conference for Allograft Pathology regarding diagnostics of chronic T-cell mediated rejection, inflammation in interstitial fibrosis and tubular atrophy, and antibody-mediated rejection

Carmona-escamilla MA, et al. (2018). Peripheral blood regulatory T cells are diminished in kidney transplant patients with chronic allograft nephropathy. *Transplant Proc.* 50(2):444-448. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/29579824>

- Assessed peripheral blood for CD4+CD25+FOXP3+ regulatory T cell (Treg) levels in patients with chronic allograft nephropathy (CAN) 1 year after kidney transplantation
- Found low frequency of Tregs in peripheral blood from renal transplant patients with CAN suggests unfavorable prognosis for allograft immune tolerance

Medeiros, M. et al. (2017). Randomized controlled trial of mineralocorticoid receptor blockade in children with chronic kidney allograft nephropathy. *Clinical Journal of the American Society of Nephrology*, 12(8), 1291–1300. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/28536123/>

- Prospective, randomized single blind study of 24 pediatric kidney transplant recipients with biopsy-proven chronic allograft nephropathy and adequate graft function (eGFR > 40 mL/min per 1.73 m²). Subjects had calcineurin inhibitor reduction by 20% and were randomized to parallel arms of either eplerenone or placebo. Primary outcome was change in eGFR after 24 months and biopsies were performed at 24 months.
- Between-group change in eGFR from baseline (-14 mL/min per 1.73 m² placebo vs -5 mL/min per 1.73 m² eplerenone) was not significantly different between groups. Patients in the placebo arm experienced higher percentage of segmental glomerulosclerosis and total glomerulosclerosis at 24 months. Albumin-to-creatinine ratio was not significantly different at 24 months but was numerically stable from baseline in eplerenone and increased in placebo groups. There were no significant changes in serum potassium concentrations throughout the study.
- The investigators concluded that this study was underpowered to detect clinical effect of eplerenone administration on chronic allograft nephropathy, but that there was associated benefit in structural injury.

Riella LV, Djamali A, Pascual J. (2017). Chronic allograft injury: Mechanisms and potential treatment targets. *Transplant Rev (Orlando)*.31(1),1-9. Retrieved from: <https://www.sciencedirect.com/science/article/pii/S0955470X16300532>

- This review article provides an overview of the association of nonadherence, antibody-mediated injury, disease recurrence, and BK nephropathy to chronic allograft nephropathy. Strategies to manage patients experiencing CAN are also included in this article.
 - Potential strategies to minimize CAN are CNI minimization, better preservation of allograft after retrieval, use of protocol biopsies, active nonadherence screening, measurement of DSA posttransplant, HTN, HLD, and hyperglycemia management

Vanhove, T. et al. (2016). High inpatient variability of tacrolimus concentrations predicts accelerated progression of chronic histologic lesions in renal recipients. *American Journal of Transplantation*. 16(10), 2954–2963. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/27013142/>

- Single-center observational retrospective cohort analysis of tacrolimus coefficient of variability (CV) among 220 kidney transplant recipients and association with chronic lesions.
- Subjects were grouped into three CV tertiles (cutoffs 14.4% and 22.1%). Recipients in the highest CV tertile had an increased risk of moderate to severe fibrosis and tubular atrophy by 2 years compared with the low CV tertile and higher chronicity score than in the middle and low tertiles. However, this increase in chronic histologic lesions was not accompanied by a decrease in renal function, which was significantly better at 2 years than at 3 months.

De Sandes- Freitas TV, et al. (2015). Subclinical lesions and donor-specific antibodies in kidney transplant recipients receiving tacrolimus-based immunosuppressive regimen followed by early conversion to sirolimus. *Transplantation*. 99 (11). 2372 – 81. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/25929604>

- Kidney transplant recipients receiving reduced TAC exposure were studied. Subclinical inflammation lesions at 3 months were found to be associated with IF/TA at 24 months. Conversion from TAC to SRL was associated with inferior renal function, higher incidence of IF/TA, and trends to higher incidence of DSA at 24 months.
 - At baseline, interstitial fibrosis and tubular atrophy occurred at 10% and at 24 months, rose to 57.6%

Qiu Y, Wang X, Fan J, Rao Z, Lu Y, Lin T. (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/26707320>

- Systematic review of 4 RCTS evaluating conversion from calcineurin inhibitors to mTOR inhibitors in heart transplant recipients. Patients who underwent conversion had a higher creatinine clearance and lower serum creatinine levels (p=0.02). These patients had

significantly higher occurrence of adverse events, including skin diseases, GI side effects, bone marrow suppression, and infections. There was no significant difference between groups in graft rejection.

- The risk and benefits must be assessed for each patient when considering the switch between CNI to mTORi. There was improvement in renal function but had more adverse events specific to mTORi

Issa N, Kukla A, Ibrahim HN. (2013). Calcineurin inhibitor nephrotoxicity: a review and perspective of the evidence. *Am J Nephrol.* 37,602-12. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/23796509>

- The authors provided a review of the importance of calcineurin inhibitor toxicity in chronic allograft dysfunction.

Husain S, Sis B. (2013). Advances in the understanding of transplant glomerulopathy. *Am J Kidney Dis.* 62,352-63. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/23313456>

- This article describes the incidence, nature, pathology, and diagnostic approaches of chronic allograft nephropathy
- Transplant glomerulopathy is a manifestation of chronic AMR against the kidney allograft

Salleres J, et al. (2012). Understanding the causes of kidney transplant failure: The dominant role of antibody-mediated rejection and nonadherence. *Am J Transplant.* 12, 388-399. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/22081892>

- 315 kidney transplant recipients prospectively enrolled at the time of an indication based biopsy to assess cause of allograft dysfunction; range of 6 days to 32 years post-transplant
- 60 kidney transplants lead to graft failure during the follow-up period with a majority attributed to antibody mediated rejection (ABMR) or mixed rejection
- 18 of 19 patients with documented nonadherence at time of biopsy had evidence of ABMR
- 3 groups of nonrejection causes of failure: glomerulonephritis, polyomavirus nephropathy, and failure in context of an concurrent illness

Dinavahi R, et al. (2011). Antibodies reactive to non-HLA antigens in transplant glomerulopathy. *J Am Soc Nephrol.* 22,1168-78. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/21566057>

- This trial details the relative importance of non-HLA antibodies to the development of transplant glomerulopathy using microarrays.
- Highlights the strengths and limitations of large throughput protein microarray screening can be informative but has high false-positive rates

Stegall MD, et al. (2011). The histology of solitary renal allografts at 1 and 5 years after transplantation. *Am J Transplant.* 11, 698-707. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/21062418>

- This study describes the histologic changes of renal allografts using protocol biopsies at 1 and 5 years post-transplant and highlights the importance of graft injury to development of chronic changes.

John R, Konvalinka A, Tobar A, Kim SJ, Reich HN, Herzenberg AM. (2010). Determinants of long-term graft outcome in transplant glomerulopathy. *Transplantation.* 90,757-64. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/20838279>

- This retrospective trial identifies the determinants associated with graft outcome in transplant glomerulopathy.

Weir MR, Wali RK. (2009) Minimizing the risk of chronic allograft nephropathy. *Transplantation,* 87, S14-8. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/19384181>

- This review discusses risk factors for the deterioration of the kidney allograft function, and highlights caveats in current monitoring leading to chronic changes while suggesting avenues to decrease incidence of chronic allograft nephropathy.

- Calcineurin inhibitor withdrawal may be one of the most important opportunities for consideration, both in patients with established allograft nephropathy, but perhaps also even more importantly, patients in the early posttransplantation period.

Birnbaum LM, et al. (2009). Management of chronic allograft nephropathy: a systematic review. Clin J Am Soc Nephrol. 4, 860-5. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/19339427>

- This systematic review highlights the scarcity of data that surrounds the management of chronic allograft nephropathy, and the lack of consensus on how to best approach this complication. Several strategies are reviewed with a focus on immunosuppressant management.
- Potential withdrawal of CNI can lead to better long-term graft survival but more studies need to be completed

Li C, Yang CW. (2009). The pathogenesis and treatment of chronic allograft nephropathy. Nat Rev Nephrol. 5,513-9. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/19636333>

- This review details how acute rejection, donor age, new onset diabetes after transplant, hyperlipidemia, hypertension, viral infections, drug toxicity and HLA antibodies contribute to the pathogenesis of chronic allograft nephropathy.

Ekberg H, et al. (2009). Calcineurin inhibitor minimization in the Symphony study: observational results 3 years after transplantation. (ELITE-Symphony trial 3-year follow-up). Am J Transplant. 9(8),1876-85. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/19563339>

- Additional follow-up for 2 more years observationally after ELITE-Symphony trial. Renal function remained stable, and overall rates of death, graft loss, and acute rejection were low. MMF + low-dose tacrolimus + steroids had highest GFR, highest graft survival rate, and least acute rejection versus the other groups (see ELITE-Symphony trial above), but difference was not significant. Patients commonly switched from sirolimus to tacrolimus secondary to adverse events.

Ekberg H, et al. (2007). Reduced exposure to calcineurin inhibitors in renal transplantation. (ELITE-Symphony trial). N Engl J Med. 357(25), 2562-75. Retrieved from: <https://www.nejm.org/doi/full/10.1056/NEJMoa067411>

- 12-month long prospective, randomized, open-label, multicenter study in predominantly low-risk kidney transplant recipients who received multiple CNI-limiting strategies (standard-dose cyclosporine, daclizumab induction + low-dose cyclosporine, daclizumab induction + low-dose tacrolimus, daclizumab induction + low-dose sirolimus).
- Mean GFR higher was in tacrolimus group compared to other three groups; rate of biopsy-proven acute rejection was lower in tacrolimus group compared to other three groups; allograft survival was highest in tacrolimus group; serious adverse events were more common in sirolimus group.

Mulay, AV, et al. (2006). Conversion from calcineurin inhibitors to sirolimus for chronic renal allograft dysfunction: a systematic review of the evidence. Transplantation. 82(9), 1153–1162. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/17102766/>

- Systematic literature review of 30 studies including kidney transplant recipients converted from calcineurin inhibitor (CNI) to sirolimus for histologic or clinically presumed chronic allograft nephropathy or chronic CNI toxicity. Primary efficacy endpoints were change in renal function and proportion of patients with stabilization or improvement of renal function. Follow-up time ranged from 6-24 months.
- Pooled estimate showed improved change in creatinine clearance from baseline after conversion to sirolimus in 4 randomized (6.4 mL/min; 95% CI 1.9-11.0 mL/min; p=0.006) and 6 nonrandomized studies (5.7 mL/min; 95% CI 1.4-10.1 mL/min; p=0.003). Pooled estimate of 10 nonrandomized studies showed improved or stabilized renal function in 66% (95% CI 61-72%).
- Cholesterol and triglyceride levels were significantly increased in pooled estimate and discontinuation rates due to adverse effects were 28% (95% CI 0-59%) in randomized trials and

17% (95% CI 12-22%) in nonrandomized studies. Acute rejection occurred in 3.4% of patients in 15 nonrandomized studies

Nankivell BJ, Borrows RJ, Fung CLS, O'connell PJ, Allen RDM, Chapman JR. (2003). The Natural History of Chronic Allograft Nephropathy. *N Engl J Med.* 349, 2326-33. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/14668458>

- This prospective study details the progression of CAN based in type 1 diabetic patients having received simultaneous kidney-pancreas transplantation. Biopsy samples were collected for 10 years on a perprotocol based approach.
- 2 stage treatment may be preferable in optimizing therapy to prevent CAN o Early stage: maximize calcineurin inhibitor to minimize early immunologic injury o Late stage: non-nephrotoxic immunosuppression can be implemented

8.7. Hemolytic uremic syndrome (HUS)/Thrombotic thrombocytopenic purpura (TTP)

Gurevich E, et al. (2023). Pharmacological management of atypical hemolytic uremic syndrome in pediatric patients: current and future. *Pediatric Drugs*, 25, 193-202. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9839393/>

- Review of current therapies for atypical HUS in pediatric patients, including the monoclonal C5 antibodies eculizumab and newly approved ravulizumab.

Mazzierli T, et al. (2023). Drug-induced thrombotic microangiopathy: an updated review of causative drugs, pathophysiology, and management. *Frontiers in Pharmacology*, 13. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9868185/>

- Review of drug-induced causes of thrombotic microangiopathy (TMA), including immunosuppressive and anti-infective medications used in transplant. The article also discusses the role of plasmapheresis, rituximab, and anti-complement therapy for treatment of drug-induced TMA.

Suenaga A, et al. (2023). A case of antiphospholipid syndrome nephropathy with acute thrombotic microangiopathy after renal transplantation. *Intern Med Advance Publication*, 10.2169/internalmedicine.0813-22. Retrieved from <https://pubmed.ncbi.nlm.nih.gov/36725047/>

- A case report of a 36-year-old male with history of lupus nephritis and antiphospholipid syndrome (APS) status post living-related renal transplant who experienced graft loss due to HUS. Biopsy showed TMA likely associated with APS.

Ter Avest M, et al. (2023). Proposal for individualized dosing of eculizumab in atypical haemolytic uraemic syndrome: patient friendly and cost effective. *Nephrol Dial Transplant*, 38, 362-371. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/35238929/>

- Eculizumab for the treatment of atypical HUS in adults is administered as a fixed dose and at fixed dosing intervals. However, interindividual variability in pharmacokinetics (PK) and pharmacodynamics (PD) may lead to subtherapeutic drug levels in some patients. This article presents the results of an add-on study to CUREiHUS (NTR5988/NL5833) to develop a population PK-PD model for eculizumab and explore alternative individualized dosing strategies.

AlZabali S, et al. (2022). A Multicenter Study Evaluating the Discontinuation of Eculizumab Therapy in Children with Atypical Hemolytic Uremic Syndrome. *Children (Basel, Switzerland)*, 9(11), 1734. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/36421183/>

- Multicenter retrospective study pediatric patients who were diagnosed with aHUS and who discontinued eculizumab between June 2013 and June 2021 to assess the rate and risk factors of aHUS recurrence.

Glover, et al. (2022). Assessing the Impact of Prophylactic Eculizumab on Renal Graft Survival in Atypical Hemolytic Uremic Syndrome. *Transplantation*, 10.1097/TP.0000000000004355. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/36413152/>

- Retrospective case review describing transplant outcomes in patients with aHUS transplanted between 1978 and 2017. Prophylactic eculizumab treatment improved renal allograft survival ($P = 0.006$) in medium and high-risk recipients with 1-y survival of 97% versus 64% in untreated patients.

Ijiri, et al. (2022). Basiliximab for early perioperative transplant-associated thrombotic microangiopathy after lung transplantation: a case report. *Surgical case reports*, 8(1), 187. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/36173476/>

- This case report discusses a patient who received a lung transplant and developed transplant-associated thrombotic microangiopathy 6 days post-op and tacrolimus was thought to be the causal agent. Tacrolimus was stopped and basiliximab administered. On post-op day 14, the platelet count recovered and the patient was switched from basiliximab to cyclosporine. Using this protocol, worsening thrombotic microangiopathy and acute rejection were avoided.

Tau, J, et al. (2022). Evaluation of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies: Lessons learned from a 14-year retrospective study. *Therapeutic apheresis and dialysis: official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy*, 10.1111/1744-9987.13864. Advance online publication. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35501999/>

- Descriptive 14-year review of 70 patients referred for plasma exchange with a suspected diagnosis of TTP. Fifteen of the patients were diagnosed with TTP based upon ADAMTS-13 activity with the other 51 patients having other non-TTP TMA diagnoses. The mortality rate was significant for both TTP and non-TTP TMAs. Early access to ADAMTS-13 testing is crucial to the diagnosis of the TMA. Early diagnosis benefits not only patients with confirmed TTP but those with other TMAs who, as a group, were found to have higher mortality than TTP patients.

Nga, et al. (2021). Thrombotic microangiopathy after kidney transplantation: Analysis of the Brazilian Atypical Hemolytic Uremic Syndrome cohort. *PloS one*, 16(11), e0258319. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34748552/>

- Multicenter retrospective cohort study including kidney transplant recipients with atypical HUS (aHUS). Patients were stratified into three groups: no use of eculizumab, use of eculizumab for treatment of after transplantation TMA, and use of eculizumab for prophylaxis of aHUS recurrence.
- The TMA graft loss in the absence of a specific complement-inhibitor was higher among the Brazilian cohort of kidney transplant patients. In the no eculizumab group ($n = 11$), there was a 91% graft loss due to the TMA. The hazard ratio of TMA graft loss was 0.07 [0.01–0.55], $p = 0.012$ in the eculizumab prophylactic group and 0.04 [0.00–0.28], $p = 0.002$ in the eculizumab therapeutic group.

Özçakar, et al. (2021). Transplantation in pediatric aHUS within the era of eculizumab therapy. *Pediatric transplantation*, 25(3), e13914. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33217100/>

- Retrospective, multicenter study describing the clinical findings and outcomes of 12 pediatric aHUS patients after renal transplantation.

Ariceta, G, et al. (2021). The long-acting C5 inhibitor, ravulizumab, is effective and safe in pediatric patients with atypical hemolytic uremic syndrome naïve to complement inhibitor treatment. *Kidney international*, 100(1), 225–237. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33307104/>

- Phase III, single-arm trial evaluating the efficacy and safety of ravulizumab in complement inhibitor naïve children with atypical hemolytic uremic syndrome. Ravulizumab provided immediate, complete, and sustained complement C5 inhibition, resulting in rapid improvement in renal and hematologic parameters across 26 weeks, and further increase in response rate over longer duration, with no unexpected safety concerns.

Kant S, et al. (2020). Ten-year outcome of Eculizumab in kidney transplant recipients with atypical hemolytic uremic syndrome- a single center experience. *BMC Nephrology*. 21(1). Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32434487/>

- Retrospective analysis of 19 kidney transplant recipients (36 total allografts) at a single center with a clinical diagnosis of atypical hemolytic uremic syndrome (aHUS). aHUS recurrence, death-censored graft loss, and renal function at last follow up was evaluated in patients who did or did not receive aHUS prophylaxis with eculizumab.
- Recurrent aHUS occurred in 70% of allografts without eculizumab prophylaxis; no recurrence occurred subjects receiving eculizumab prophylaxis ($p < 0.001$). Graft failure occurred in 44% vs 10% with eculizumab prophylaxis ($p=0.09$). Estimated glomerular filtration rate did not differ significantly between both groups.

Zheng XL, et al. (2020). ISTHL guidelines for the diagnosis of thrombotic thrombocytopenic purpura. *Journal of Thrombosis and Haemostasis*. 18(10), 2486–2495. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/32914582/>

- Guidelines from the international society on thrombosis and haemostasis on diagnosis and management of acute thrombotic thrombocytopenic purpura.

Bascunana A, et al. (2020). Thrombotic microangiopathy in a kidney transplant patient with COVID-19. *Kidney Med*. 3(1),124-7.

- Case report of a kidney transplant recipient who developed severe thrombotic microangiopathy and acute kidney injury concurrent with acute COVID-19 infection

Bayer G, et al. (2019). Etiology and outcomes of thrombotic microangiopathies. *Clinical Journal of the American Society of Nephrology*. 14(4), 557–566. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/30862697/>

- Retrospective study of 564 patients with thrombotic microangiopathies (TMAs) describing the incidence, relative contribution, management, and prognosis.
- Common causes of secondary TMA included transplantation (18%) and drugs (27%), including calcineurin inhibitors.

Tatapudi VS, Lonze BE, Wu M, Montgomery RA. (2018). Early conversion from tacrolimus to belatacept in a highly sensitized renal allograft recipient with calcineurin inhibitor-induced de novo post-transplant hemolytic uremic syndrome. *Case Rep Nephrol Dial*. 8(1), 10-19. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/29594146>

- This case report details the course of a highly-sensitized renal transplant recipient with pretransplant DSA successfully converted from tacrolimus to belatacept within 1 week of transplant, secondary to the diagnosis of CNI-induced de novo HUS.

Olson S, et al. (2018). When to stop eculizumab in complement-mediated thrombotic microangiopathies. *American Journal of Nephrology*. 48(2), 96–107. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/30110670/>

- Review of categories of thrombotic microangiopathies, evidence for eculizumab use for each indication, and monitoring parameters for eculizumab discontinuation.

Duineveld C, Verhave JC, Berger SP, Van de kar NCAJ, Wetzels JFM. (2017). Living Donor Kidney Transplantation in Atypical Hemolytic Uremic Syndrome: A Case Series. *Am J Kidney Dis*. 70(6), 770-777. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28821363>

- This case series describes 17 patients who underwent living donor kidney transplantation and received eculizumab prophylaxis due to documented post transplantation recurrent thrombotic microangiopathy. One patient had aHUS recurrence 68 days post-transplant, which was successfully treated with eculizumab. 3 patients were treated for rejection, and 2 patients developed BK nephropathy.

Saha M, Mcdaniel JK, Zheng XL. (2017). Thrombotic thrombocytopenic purpura: pathogenesis, diagnosis and potential novel therapeutics. *J Thromb Haemost.* 15(10),1889-1900. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/28662310>

- This review highlights recent progress in the pathogenesis, diagnosis, and current and potential novel therapies for hereditary and acquired TTP.

Kasapoğlu U, et al. (2015). Prophylactic eculizumab use in kidney transplantation: A review of the literature and report of a case with atypical hemolytic uremic syndrome. *Ann Transplant.* 20, 714 – 719. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/26621268>

- This case report discusses a patient who received a kidney transplant secondary to aHUS. This patient received eculizumab weekly for one-month post-transplant, and the patient completed one year of follow-up with an uneventful post-transplant course.

Tsai, HM. (2013). Thrombotic Thrombocytopenic Purpura and the Atypical Hemolytic Uremic Syndrome An Update. *Hematol Oncol Clin N Am.* 27, 565-584. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/23714312>

- This article provides a review of the etiology, pathology and treatments for TTP and aHUS in nontransplant patients.
- TTP and aHUS are chronic diseases that present with thrombocytopenia and microangiopathic hemolysis but have different pathology and pathogenesis and thus require different therapeutic approaches

Noris M, Remuzzi G. (2013). Managing and preventing atypical hemolytic uremic syndrome recurrence after kidney transplantation. *Curr Opin Nephrol Hypertens.* 22, 704-712. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/24076560>

- This review highlights the risk of recurrence of aHUS following kidney transplantation and discusses the roles of plasma exchange and eculizumab therapy to prevent recurrence.
- Patients with specific genetic abnormalities (CFH, CFI, C3, CFB) of aHUS will most likely need posttransplant eculizumab prophylaxis

Kavanagh D, Goodship TH, Richards A. (2013). Atypical Hemolytic Uremic Syndrome. *Semin Nephrol,* 33, 508-530. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/24161037>

- This reviews the pathology of aHUS, role of complement and genetic abnormalities contributing to aHUS in non-transplant patients. It also reviews extrarenal manifestations. Lastly, the role of liver-kidney transplantation for the syndrome and de novo aHUS after renal transplantation are addressed.

Carson JM, Newman ED, Farber JL, Filippone EJ. (2012). Tacrolimus-induced thrombotic microangiopathy: natural history of a severe, acute vasculopathy. *Clinical Nephrol.* 77, 79-84. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/22185974>

- This case report details the natural progression of TMA in a tacrolimus-treated patient and provides a brief narrative review of the history of TMA in transplantation.

Yilmaz VT, Kocak H, Avedi AB, Salim O, Ersoy FF, Suleymanlar G. (2011). Thrombotic thrombocytopenia purpura associated with everolimus use in a renal transplant patient. *Int Urol Nephrol.* 43, 581-584. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/20495869>

- This case report provides supporting evidence that TTP can be associated with everolimus use in a sirolimus-conversion kidney transplant recipient.

Lovric S, et al. (2011). Combination of everolimus with calcineurin inhibitor medication resulted in post-transplant haemolytic uraemic syndrome in a lung transplant recipients - a case series. *Nephrol Dial Transplant.* 26, 3032-3038. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/21310739>

- This retrospective case series identified lung transplant patients who experienced aHUS post-transplant in an mTOR- and CNI-combination regimen. Risk factors are also discussed.

Parissis H, Gould K, Dark J. (2010). Dangerous drug interactions leading to hemolytic uremic syndrome following lung transplantation. *J Cardiothorac Surg.* 5,70-73. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/20813025>

- These 2 case reports highlight the potential importance of macrolide-tacrolimus drug-drug interaction leading to increased peak tacrolimus levels. This resulted in aHUS in lung transplant recipients.

Saland JM, et al. (2009). Liver-Kidney Transplantation to Cure Atypical Hemolytic Uremic Syndrome. *J Am Soc Nephrol.* 20, 940-949. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/19092117>

- This review article discusses the potential advantages and mechanisms surrounding simultaneous liver-kidney transplantation to cure aHUS and decrease risk of recurrence.

Qu L, Kiss JE. (2005). Thrombotic microangiopathy in transplantation and malignancy. *Semin Thromb Hemost.* 31, 691-699. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/16388420>

- This review discusses transplant-specific incidence, pathophysiology, treatment and outcomes of TMA in SOT and BMT.

Lin CC, King KL, Chao YW, Yang AH, Chang CF, Yang, WC. (2003). Tacrolimus-associated hemolytic uremic syndrome: A case analysis. *J Nephrol.* 16,580-585. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/14696762>

- This case report, followed by a review of 15 previous cases of tacrolimus-associated HUS, describes prevalence, time to onset, and outcome of the condition.

8.8 Bone and mineral disorder management

Billups SJ, et al. (2023). Bad to the bones: prescribing of drugs for the prevention and treatment of osteoporosis in patients on chronic glucocorticoids. *Archives of Osteoporosis*, 18(38), 10.1007/s11657-023-01222-0. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9976654/>

- A retrospective single center cohort study to identify risk factors for developing osteoporosis in patients receiving glucocorticoids. Of 7,774 patients included in the study, 13.2% were prescribed osteoporosis pharmacologic treatment, 31.7% were prescribed calcium, and 37.9% were prescribed vitamin D. Factors independently associated with increased odds of osteoporosis pharmacologic treatment were having osteoporosis or osteopenia on the problem list (OR=4.45, 95% CI 3.70-5.34), history of a DEXA scan (OR=2.18, 95% CI 1.82-2.62), history of fracture (OR=1.83, 95% CI 1.54-2.17), and increased duration of corticosteroid use (OR=1.33, 95% CI 1.10-1.59).

Monteiro SS, et al. (2023). Bone mineral density progression following long-term simultaneous pancreas-kidney transplantation in type-1 diabetes. *Ann Endocrinol*, /10.1016/j.ando.2023.03.002. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/36931500/>

- A retrospective cohort study aimed at assessing bone mineral density and long-term progression of bone disorders in patients with type 1 diabetes undergoing simultaneous pancreas-kidney transplantation. Seventy-three patients were included in the study. At 4-year follow-up after transplantation, bone mineral density was significantly improved at the lumbar spine (P<0.001) and femoral neck (P=0.01). Male gender (OR 10.82, 95% CI 2.88-40.70) and low BMI (OR 0.73, 95% CI 0.55-0.97) were significantly associated with lumbar but not femoral osteoporosis.

Tran TVM, et al. (2023). Bone health outcomes in post-lung transplant patients with cystic fibrosis. *J Cyst Fibrosis*, S1569-1993(23)00005-X. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/36669961/>

- A retrospective chart review of lung transplant patients with and without cystic fibrosis (CF) to investigate the long-term changes in bone mineral density and fracture incidence after transplantation. Pre-transplant, patients with CF were younger, had lower BMI, and had lower baseline Z-scores at the lumbar spine, femoral neck, and total hip (P<0.001). Post-transplant, CF

patients had better bone mineral density recovery but there was no difference in rate of post-transplant fractures when compared to non-CF patients.

Tsujita, et al. (2022). Cholecalciferol Supplementation Attenuates Bone Loss in Incident Kidney Transplant Recipients: A Prespecified Secondary Endpoint Analysis of a Randomized Controlled Trial. *Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research*, 37(2), 303–311. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34747516/>

- This pre-specified secondary endpoint analysis of a randomized controlled trial evaluated changes in PTH, bone metabolic markers, and bone mineral density (BMD). At 1 month post-transplant, patients were randomized to an 11-month intervention with cholecalciferol (4000 IU/d) or placebo. 4000 IU/d cholecalciferol significantly reduced PTH levels and attenuated lumbar spine bone mineral density loss after kidney transplant.

Khairallah, et al. (2022). Bone and Mineral Disease in Kidney Transplant Recipients. *Clinical journal of the American Society of Nephrology: CJASN*, 17(1), 121–130. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34127484/>

- Review of the epidemiology, effect, and treatment of metabolic and skeletal derangements in the transplant recipient.

Korucu, et al. (2022). The Effects of CNI and Mtor-Based Regimens on Bone Mineral Density After Renal Transplantation. *Priloz*: 43(1), 101–107. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/35451298/>

- Retrospective observational cohort study evaluating the bone mineral density (BMD) changes in renal transplant patients under CNI or mTORi-based maintenance regimens during the first five-year post-transplant course.
- Results suggest that CNI-based treatment is associated with decreased femur neck BMD scores, and mTORi-based treatment tends to be beneficial in the post-transplant five-year follow-up.

Abulmeaty, M, et al. (2021). Impact of Vitamin D Supplementation on Bone Mineral Density and All-Cause Mortality in Heart Transplant Patients. *Biomedicine*, 9(10), 1450. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/34680567/>

- Study investigating the association of vitamin D levels and bone mineral density (BMD) with all-cause mortality in heart transplant patients over two years. Supplementation with VD3 10,000 IU daily dose, Ca 1200 mg/day, and Mg 200 mg/day were effective in elevating the serum level of 25OHVD. However, no significant impact was detected on the preservation of the BMD at measured sites, or on correction of tertiary hyperparathyroidism. The 25OHVD failed to improve the all-cause mortality hazard ratio.

Vanderstraetan K, et al. (2021). Body mass index is associated with hyperparathyroidism in pediatric kidney transplant recipients. *Pediatr Nephrol*. 36, 977-86. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33034742/>

- Longitudinal, retrospective study of 149 pediatric de novo kidney transplant recipients evaluating the one-year natural history of parathyroid hormone and identifying risk factors for persistent hyperparathyroidism
- The probability of hyperparathyroidism and severe hyperparathyroidism declined from 0.49 and 0.17 to 0.29 and 0.09 at 3 and 12 months after transplantation, respectively.
- BMI SDS, eGFR and pre-transplant hyperparathyroidism were associated with hyperparathyroidism 12 months after transplantation.
- Pre-transplant hyperparathyroidism was associated with severe hyperparathyroidism at 9 months after transplantation.

Kusumi K, Shaikhkhalil A, Patel HP, Mahan JD. (2021). Promoting bone health in children and adolescents following solid organ transplantation. *Pediatr Transplant*. 25,e13940. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/33341105/>

- Review of measures for promoting bone health in children and adolescents, dietary factors associated with bone health, the impact of immunosuppressive medications on bone and anti-resorptive and anabolic therapies.

Palmer, S. C. et al. (2019). Interventions for preventing bone disease in kidney transplant recipients. Cochrane Database of Systematic Reviews. (10). Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/31637698/>

- Meta-analysis and systematic review from Cochrane Kidney and Transplant Register of 45 randomized/quasi-randomized controlled trials evaluating treatments for bone disease among kidney transplant recipients with the primary efficacy outcome of bone fracture.
- Risk of bias were high and there was generally low certainty of evidence. There was little to no evidence to support the use of vitamin D, teriparatide, denosumab, cinacalcet, or calcitonin to prevent skeletal complications. Compared to placebo, bisphosphonates may prevent fracture at 12 months (RR 0.62, 95% CI 0.38 to 1.01) and may reduce bone pain (RR 0.20, 95% CI 0.04 to 0.93).

Bonani, M. et al. (2016). Effect of twice-yearly denosumab on prevention of bone mineral density loss in de novo kidney transplant recipients: A randomized controlled trial. *American Journal of Transplantation*, 16(6), 1882–1891. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/26713403/>

- Open-label, prospective, randomized trial of 90 de novo kidney transplant recipients who received denosumab 60 mg at baseline and again at 6 months or no treatment. Patients with severe osteoporosis, severe hyper- or hypoparathyroidism, or hypo- or hypercalcemia were excluded. Primary endpoint was percentage change in baseline areal BMD at the total lumbar spine at 12 months.
- Compared to no treatment, denosumab was significantly associated with increased areal BMD at the total lumbar spine (between-group difference 5.1%, $p < 0.0001$) and total hip (between-group difference 1.9%, $p = 0.035$) at 12 months. Urinary tract infections and diarrhea occurred more frequently in the denosumab group.

Bouquegneau, A. et al. (2016). Bone Disease after Kidney Transplantation. *Clinical Journal of the American Society of Nephrology*. 11(7), 1282–1296. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/26912549/>

- Review of epidemiology and pathophysiology of post-transplantation bone disease, options for evaluating fracture risk, and strategies for treatment and prevention

Cohen, J. B. et al. (2012). Cinacalcet for the treatment of hyperparathyroidism in kidney transplant recipients: a systematic review and meta-analysis. *Transplantation*, 94(10), 1041–1048. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/23069843/>

- Systematic review and meta-analysis of 21 studies with 411 kidney transplant recipients evaluating cinacalcet for the treatment of hyperparathyroidism.
- Meta-analysis revealed significant decrease in calcium (-1.14 mg/dL), increase in phosphorus (+0.46 mg/dL), and decrease in parathyroid hormone (102 pg/mL). Seven patients from 5 studies developed hypocalcemia. Calciuria greatly varied between studies. Gastrointestinal side effects were most common.

Smerud, K. T. et al. (2012). A 1-year randomized, double-blind, placebo-controlled study of intravenous ibandronate on bone loss following renal transplantation. *American Journal of Transplantation*, 12(12), 3316–3325. Retrieved from: <https://pubmed.ncbi.nlm.nih.gov/22946930/>

- Randomized, double-blind trial of kidney transplant recipients maintained on calcium and calcitriol at a single-center who received either additional ibandronate or placebo. Change from baseline in lumbar spine bone mineral density (BMD) was evaluated at 12 months.
- Results: At 12 months, relative change in BMD in the lumbar spine was not significantly different between ibandronate and placebo groups at +1.5% and +0.5% respectively ($p = 0.33$). However, there was a modest significant difference in change in BMD in the total femur, ultradistal radius,

and total body. Incidence of adverse events was statistically similar between groups. However, this study was not powered to determine effect on fracture risk.