8. Additional organ-specific considerations

8.1. Cardiac allograft vasculopathy (CAV)

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 ± / 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 ≥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 (± 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) (ΔMaximal Intimal Thickness 0.03 ± 0.06 and 0.08 ± 0.12 mm, ΔPercent Atheroma Volume 1.3 ± 2.3 and 4.2 ± 5.0%, ΔTotal Atheroma Volume 1.1 ± 19.2 mm^3 and 13.8 ± 28.0 mm^3 [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 mofeil for the composite outcome of biopsy-proven acute rejection of ISHLT grade≥ 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.nl8.m.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 (≥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 ± 2.2% vs. 19.0 ± 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

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 mm^3 vs. 177.3 ± 94.3 mm^3, 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 Phancao 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 m^3 higher eGFR at levels below 45 ml/min/1.73 m^3 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 m^3.
- 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/new onset diabetes after transplant

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 asses 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. Reetrieved 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

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 m(2) in the CsA-ME cohort and 65.9 +/- 23.1 mL/min/1.73 m(2) 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

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

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, Kušnírová 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

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 m^2). 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 m^2 placebo vs -5 mL/min per 1.73 m^2 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 intrapatient 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)

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, Aveci 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

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.