

1. Kidney transplantation

1.1. Induction therapy

Brennan, DC et al. (2006) Rabbit Antithymocyte Globulin versus Basiliximab in Renal Transplantation. New England Journal of Medicine, 355: 1967-77. Retrieved from:
<http://www.ncbi.nlm.nih.gov/pubmed/17093248>.

- High risk patients receiving a transplant from a deceased donor had reduced incidence and severity of acute rejection when induction was done with antithymocyte globulin when compared to basiliximab.

Ciancio, G et al. (2008) Alemtuzumab (Campath-1H) in Kidney Transplantation. American Journal of Transplantation, 8:15-20. Retrieved from:
<http://www.ncbi.nlm.nih.gov/pubmed/18093269>.

- Mini-review regarding use of alemtuzumab in kidney transplant, including site experiences.

Ejaz NS, Shields AR, Alloway RR, et al. Randomized controlled pilot study of B cell-targeted induction therapy in HLA sensitized kidney transplant recipients. Am J Transplant. 2013;13(12):3142-54. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/24266968>

- Prospective, randomized study evaluating the addition of B cell/plasma cell-targeting agents to T cell-based induction with rabbit antithymocyte globulin (rATG) in high immunologic risk renal transplant recipients (n=40). Patients were randomized to induction with rATG, rATG + rituximab, rATG+ bortezomib or rATG + rituximab + bortezomib. No difference in patient survival, renal allograft survival, and renal allograft function at one year post-transplant was observed.

Farney AC, Doares W, Rogers J, et al. A randomized trial of alemtuzumab versus antithymocyte globulin induction in renal and pancreas transplantation. *Transplantation*. 2009;88(6):810-9. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/19920781>

- Prospective randomized single-center trial comparing alemtuzumab and rATG induction in adult kidney and pancreas transplantation in patients (n=122). Biopsy-proven acute rejection (BPAR) episodes occurred in 16 (14%) alemtuzumab patients compared with 28 (26%) rATG patients (P < 0.02). Infections and malignancy were similar between the two induction arms. Alemtuzumab was associated with less BPAR than rATG induction.

Gabardi, S et al. Induction Immunosuppressive Therapies in Renal Transplantation. *American Journal of Health-Systems Pharmacist*, 2011;68:211-8. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/21258026>.

- A review article discussing the therapeutic agents available for induction therapy.

Hanaway, MJ et al (2011) Alemtuzumab induction in renal transplantation. *New England Journal of Medicine*, 364(20):1909-19. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/21591943>.

- Superiority trial of alemtuzumab as an induction agent. Rates of acute rejection were less frequent with alemtuzumab in low risk transplant recipients when compared to basiliximab and antithymocyte.

Haynes R, Harden P, Judge P, et al. Alemtuzumab-based induction treatment versus basiliximab-based induction treatment in kidney transplantation (the 3C Study): a randomised trial. *Lancet*. 2014;384(9955):1684-90. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pubmed/25078310>

- Randomly assigned 852 kidney transplant recipients to induction treatment with alemtuzumab (followed by low-dose tacrolimus and mycophenolate without steroids) or basiliximab (followed by standard-dose tacrolimus, mycophenolate, and prednisolone). The primary outcome was biopsy-proven acute rejection at 6 months. In the alemtuzumab group 31 (7%) patients vs 68 (16%) patients in the basiliximab group; (HR 0.42, 95% CI 0.28–0.64; log-rank p<0.0001) had biopsy-proven acute rejection. No difference in treatment effect on transplant failure, serious infection, or death. Alemtuzumab induction therapy reduced the risk of biopsy-proven acute rejection at 6 months in kidney transplant recipients.

Jordan, SC et al. (2003) Intravenous immune globulin treatment inhibits crossmatch positivity and allows for successful transplantation of incompatible organs in living-donor and cadaver recipients. *Transplantation*, 76(4):631-636. Retrieved from:
<http://www.ncbi.nlm.nih.gov/pubmed/12973100>.

- Discusses the use of IVIG to decrease or eliminate cross match positivity and allow for successful transplantation.

1.2. Maintenance therapy

Budde K, Lehner F, Sommerer C, et al. Five-year outcomes in kidney transplant patients converted from cyclosporine to everolimus: the randomized ZEUS study. *Am J Transplant*. 2015;15(1):119-28. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/25521535>

- Multi-center study of kidney allograft recipients randomized to continuing cyclosporine (CsA) or converting to everolimus at 4.5 months post-transplant (n=300). At 5 years, adjusted eGFR was 66.2 mL/min/ 1.73m² with everolimus vs 60.9 mL/min/1.73m² with CsA; p<0.001.

- Cumulative incidence of biopsy-proven acute rejection was 13.6% with everolimus vs. 7.5% with CsA ($p < 0.095$); although this difference did not affect long-term graft function.
- Conversion to everolimus is associated with a significant improvement in renal function that is maintained to at least 5 years.
- Original ZEUS: <https://www.ncbi.nlm.nih.gov/pubmed/25070687>

Cantarovich D, Rostaing L, Kamar N, et al. Early corticosteroid avoidance in kidney transplant recipients receiving ATG-F induction: 5-year actual results of a prospective and randomized study. *Am J Transplant*. 2014;14(11):2556-64. Retrieved from:
<https://www.ncbi.nlm.nih.gov/pubmed/25243534>

- Randomized 197 patients to ≥6-month corticosteroids(CS) or no CS. One- and five-year graft survival (censored for death), freedom from clinical and biopsy-proven rejection, and renal function was similar between both groups. In patients receiving CS, rejections occurred later and with a higher risk for subsequent graft failure, whereas rejections in no-CS patients occurred early after transplantation and did not impair long-term renal function. More CS patients developed diabetes, dyslipidemia and malignancies.

Chadban SJ, Eris JM, Kanellis J, et al. A randomized, controlled trial of everolimus-based dual immunosuppression versus standard of care in de novo kidney transplant recipients. *Transpl Int*. 2014;27(3):302-11. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pubmed/24279685>

- Prospective, multinational, controlled trial randomized 126 de novo kidney transplant recipients to: (1)CNI-withdrawal (WD): cyclosporine +mycophenolate + steroids for the first 14 days then everolimus +

mycophenolate; (2)everolimus +mycophenolate (terminated prematurely due to excess discontinuation); (3)Control: cyclosporine + mycophenolate +steroids. Mean eGFR at 1 year for CNI-WD vs control was non-inferior (65.1 ml/min/1.73 m² vs. 67.1 ml/min/1.73 m², P = 0.026). CNI-WD group had a higher rate of BPAR (31% vs. control 13%, P = 0.048). At 1 year, CNI-WD was non-inferior in eGFR, but was associated with higher rates of acute rejection.

Durrbach, A et al. (2010). A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT Study). American Journal of Transplantation, 10, 547-57. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/20415898>.

- In extended criteria donor (ECD) kidney transplant recipients, de novo belatacept regimens improved renal function at 1 year post-transplant and metabolic endpoints compared to cyclosporine-treated patients with similar patient and graft survival and acute rejection episodes. Belatacept was associated with more cases of post-transplant lymphoproliferative disorders (PTLD), particular in patients that were EBV seronegative.

Durrbach A, Pestana JM, Florman S, et al. Long-Term Outcomes in Belatacept- Versus Cyclosporine-Treated Recipients of Extended Criteria Donor Kidneys: Final Results From BENEFIT-EXT, a Phase III Randomized Study. Am J Transplant. 2016;16(11):3192-3201.

Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/27130868>

- Extended criteria donor kidney recipients were randomized to receive belatacept-based (more intense [MI] or less intense [LI]) or cyclosporine-based immunosuppression. Mean eGFR was 53.9, 54.2, and 35.3 mL/min per 1.73 m² for belatacept MI, belatacept LI and cyclosporine, respectively (p <

0.001). Acute rejection rates, graft loss, and death were similar between groups.

Ekberg, H et al. (2007). Reduced exposure to calcineurin inhibitors in renal transplantation. New England Journal of Medicine, 357, 2562-75. Retrieved from:
<http://www.ncbi.nlm.nih.gov/pubmed/18094377>.

- Evaluation of the safety and efficacy of various immunosuppressive regimens, including standard-dose cyclosporine, standard-dose tacrolimus, low-dose tacrolimus, or low-dose sirolimus, in combination with daclizumab induction, mycophenolate mofetil, and corticosteroids. Renal function and biopsy-proven acute rejection rates were statistically lower in the low-dose tacrolimus group and, moreover, this group experienced the best overall graft survival.

Gaston, RS et al. (2001). Maintenance immunosuppression in the renal transplant recipient: an overview. American Journal of Kidney Diseases, 38, S25-35. Retrieved from:
<http://www.ncbi.nlm.nih.gov/pubmed/11729003>.

- Overview of maintenance immunosuppression in renal transplantation (calcineurin inhibitors, anti-metabolites, corticosteroids, sirolimus), including considerations regarding adverse events, drug interactions, and immunosuppressive regimens in special populations.

Gonwa, T et al. (2003). Randomized trial of tacrolimus + mycophenolate mofetil or azathioprine versus cyclosporine + mycophenolate mofetil after cadaveric kidney transplantation: results at three years. Transplantation, 75, 2048-53. Retrieved from:
<http://www.ncbi.nlm.nih.gov/pubmed/12829910>.

- A comparison of initial immunosuppressive regimens in kidney transplant recipients. Patients receiving tacrolimus-based regimens experienced

superior renal function at 1 and 3 years; in African Americans and patients with delayed graft function (DGF), the combination of tacrolimus and mycophenolate mofetil was associated with superior graft outcomes.

Haller MC, Royuela A, Nagler EV, Pascual J, Webster AC. Steroid avoidance or withdrawal for kidney transplant recipients. Cochrane Database Syst Rev. 2016;(8):CD005632.

Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/27546100>

- Cochrane review of 48 studies (n=7803 patients) evaluated three different comparisons: steroid avoidance or withdrawal vs. steroid maintenance and steroid avoidance vs. steroid withdrawal.
- No significant difference in mortality or graft loss, but steroid avoidance and withdrawal was associated with significant increase in the risk of acute rejection. Long-term consequences of steroid avoidance and withdrawal remains unclear due to lack of prospective long-term studies.

Halloran, PF et al. (2004). Immunosuppressive drugs for kidney transplantation. New England Journal of Medicine, 351, 2715-29. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/15616206>.

- Review article of the immune response and common immunosuppressive agents used for maintenance and induction therapy in kidney transplantation. Describes the classic three-signal model of T-helper cell activation and the role of immunosuppressants within this response.

Ho, ET al. (2013). Once-daily extended-release versus twice-daily standard-release tacrolimus in kidney transplant recipients: a systematic review. Transplantation, 95, 1120-28. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/23542469>.

- Systematic review (6 randomized, controlled trials; 15 observational studies) comparing once-daily to twice-daily tacrolimus in de novo or

conversion studies in renal transplant recipients. Once-daily tacrolimus was found to be comparable to standard dosing at 12 months post-transplant with regards to biopsy-proven acute rejection, patient survival, and graft survival.

KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients. (2009).

Supplement 3, Volume 9. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/19845597>

- Guidelines released from the Journal of the American Society of Transplantation (AST) and the American Society of Transplant Surgeons (ASTS). Chapters 2 and 3 describe recommendations for initial and long-term maintenance immunosuppression medications, respectively.

Knight, SR et al. (2009). Mycophenolate mofetil decreases acute rejection and may improve graft survival in renal transplant recipients when compared with azathioprine: a systematic review. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/19300178>.

- Systematic review of mycophenolate mofetil versus azathioprine in calcineurin inhibitor-containing regimens (cyclosporine, cyclosporine microemulsion, tacrolimus). Mycophenolate mofetil significantly reduced the risk of acute rejection episodes regardless of calcineurin inhibitor (RR 0.62, p<0.01), and improved graft survival (RR 0.76, p=0.04).

Lim WH, Eris J, Kanellis J, et al. A systematic review of conversion from calcineurin inhibitor to mammalian target of rapamycin inhibitors for maintenance immunosuppression in kidney transplant recipients. Am J Transplant. 2014;14(9):210-19.

Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/25088685>

- Systematic review of 29 randomized controlled trials comparing delayed conversion of mTOR for CNIs versus CNI continuation in kidney

transplantation. Patients converted to mTOR up to 1 year post-transplant had higher GFR compared with those remaining on CNI, $p < 0.001$. However, the risk of rejection at 1 year and discontinuation secondary to adverse events was higher for mTORs.

Lo, A et al. (2004). Comparison of sirolimus-based calcineurin inhibitor-sparing and calcineurin inhibitor-free regimens in cadaveric renal transplantation. *Transplantation* 77, 1228-35. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/15114090>.

- A comparison of de novo sirolimus in combination with reduced dose tacrolimus (CI-sparing regimen) or mycophenolate mofetil (CI-free regimen) in high-risk deceased donor kidney transplant recipients. While patient survival, graft survival, and incidence of acute rejection episodes were similar, the CI-sparing group experienced a higher prevalence of chronic allograft nephropathy and a lower mean estimated creatinine clearance at 1 year.

Masson P, Henderson L, Chapman JR, Craig JC, Webster AC. Belatacept for kidney transplant recipients. *Cochrane Database Syst Rev*. 2014;(11):CD010699. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/25416857>

- Cochrane review of five studies ($n=1535$) comparing belatacept and CNIs. Up to three years following transplant, belatacept and CNI-treated recipients were at similar risk of graft loss, acute rejection, and death. Belatacept is associated with better kidney transplant function, blood pressure and lipid profile and a lower incidence of diabetes versus treatment with a CNI.

Rostaing, L et al. (2011). Switching from calcineurin inhibitor-based regimens to a belatacept-based regimen in renal transplant recipients: a randomized phase II study.

Clinical Journal of the American Society of Nephrology, 6, 430-9. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/21051752>.

- Conversion from a calcineurin inhibitor-based regimen to belatacept in kidney transplant recipients (≥ 6 but ≤ 36 months post-transplant, estimated glomerular filtration rates 35-75 ml/min/1.73m²) improved renal function at 12 months but was associated with a low risk of rejection (7%) that resolved with treatment.

Rostaing L, Bunnapradist S, Grinyó JM, et al. Novel Once-Daily Extended-Release Tacrolimus Versus Twice-Daily Tacrolimus in De Novo Kidney Transplant Recipients: Two-Year Results of Phase 3, Double-Blind, Randomized Trial. Am J Kidney Dis. 2016;67(4):648-59. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/26717860>

- Multicenter, phase 3 non-inferiority trial of 543 de novo kidney recipients randomized to once daily vs. twice daily tacrolimus. Treatment failure (death, transplant failure, biopsy-proven acute rejection, or loss to follow up) and safety (adverse events, serious adverse events, new-onset diabetes, kidney function, opportunistic infections, and malignancies) was similar between the two groups at 24 months.

Schena, FP et al. (2009). Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial. Transplantation, 87, 233-42. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/19155978>.

- Eligible kidney transplant recipients (6 to 120 months post-transplant, receiving a calcineurin inhibitor after transplantation along with corticosteroids and an anti-metabolite, estimated glomerular filtration rate (GFR) > 20 ml/min/1.73m²) were stratified according to their baseline GFR

and randomly assigned to either sirolimus conversion or calcineurin inhibitor continuation. At 2 years, patients that remained on sirolimus had higher GFR, particularly in those patients with baseline GFR > 40 ml/min, and there were no differences in rejection episodes, graft survival, or patient survival. Sirolimus discontinuation rates were high and conversion was associated with more treatment-emergent adverse events.

Silva HT, Felipe CR, Garcia VD, et al. Planned randomized conversion from tacrolimus to sirolimus-based immunosuppressive regimen in de novo kidney transplant recipients. *Am J Transplant*. 2013;13(12):3155-63. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pubmed/24266969>

- Multicenter study of 297 patients initially treated with tacrolimus, mycophenolate sodium and prednisone randomized to convert to sirolimus (SRL) or continue with tacrolimus. Planned conversion to SRL at 3 months after kidney transplantation was not associated with improved renal function at 24 months. Higher mean urinary protein-to-creatinine ratio and higher incidence of treated acute rejection was observed in SRL compared to TAC group.

Thierry A, Lemeur Y, Ecotière L, et al. Minimization of maintenance immunosuppressive therapy after renal transplantation comparing cyclosporine A/azathioprine or cyclosporine A/mycophenolate mofetil bitherapy to cyclosporine A monotherapy: a 10-year postrandomization follow-up study. *Transpl Int*. 2016;29(1):23-33. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pubmed/26729582>

- Multicenter study of 204 low immunological risk kidney transplant recipients were randomized post-transplantation to receive either cyclosporine (CsA) + azathioprine (AZA), CsA + mycophenolate mofetil (MMF), or CsA

monotherapy. At 3 years, the occurrence of biopsy for graft dysfunction was similar in bitherapy and monotherapy groups, $P = 0.25$. At 10 years, patients' survival, death-censored graft survival, and mean eGFR were similar between groups. CsA monotherapy after 1 year is safe and associated with prolonged graft survival in low immunological risk kidney transplant recipients.

Vincenti, F et al. (2008). A randomized, multicenter study of steroid avoidance, early steroid withdrawal or standard steroid therapy in kidney transplant recipients. American Journal of Transplantation, 8, 307-16. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/18211506>.

- Non-highly sensitized kidney transplant recipients (first transplant, PRA < 20%, cold ischemia time < 24 hours, non-DCD) were randomized to receive no steroids, steroids until day 7 post-transplant, or standard steroid therapy. Renal function at 12 months was not significantly different; while complete steroid avoidance was associated with significantly higher rates of rejection, similar outcomes were observed with early steroid withdrawal and standard steroid therapy. Early steroid withdrawal may be an option for kidney transplant recipients not at a high rejection risk.

Vincenti, F et al. (2010). A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT Study). American Journal of Transplantation, 10, 535-46. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/20415897>.

- Kidney transplant recipients (non-ECD or DCD, PRA < 50%, re-transplant PRA < 30%) were randomized to a more intensive (MI) belatacept regimen, less intensive (LI) belatacept regimen, or cyclosporine in addition to basiliximab induction, mycophenolate mofetil, and corticosteroids.

Belatacept was associated with superior renal function, lower prevalence of chronic allograft nephropathy, improved metabolic endpoints, and similar patient and graft survival at 1 year post-transplant. Belatacept patients experienced a higher incidence of acute rejection episodes (although rejection defined as histologically-confirmed or treatment based on clinical suspicion).

Vincenti F. Belatacept and Long-Term Outcomes in Kidney Transplantation. *N Engl J Med.* 2016;374(26):2600-1. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/27355541>

- 666 renal transplant recipients were randomized to a more-intensive belatacept regimen, a less-intensive belatacept regimen, or a cyclosporine regimen. Seven years after transplantation, patient and graft survival and the mean eGFR were significantly higher with belatacept groups compared with cyclosporine.

Wagner M, Earley AK, Webster AC, Schmid CH, Balk EM, Uhlig K. Mycophenolic acid versus azathioprine as primary immunosuppression for kidney transplant recipients. *Cochrane Database Syst Rev.* 2015;(12):CD007746. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pubmed/26633102>

- Cochrane review of 23 studies (n=3301) comparing mycophenolate (MMF) and azathioprine (AZA). MMF reduced the risk for graft loss and any acute rejection, biopsy-proven acute rejection, and antibody-treated acute rejection compared to AZA. No statistically significant difference for MMF versus AZA treatment was found for all-cause mortality.

Webster, AC et al. (2005). Tacrolimus versus cyclosporine as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomized trial

data. British Medical Journal, 331, 810. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/16157605>.

- Systematic review of tacrolimus versus cyclosporine for initial maintenance immunosuppression. Tacrolimus-treated patients had lower rates of graft loss at 6 months and up to 3 years post-transplant and acute rejection at 12 months post-transplant; however, tacrolimus regimens were associated with more diabetes mellitus requiring insulin, tremor, headache, and GI upset.

Woodle, ES et al. (2005). Multivariate analysis of risk factors for acute rejection in early corticosteroid cessation regimens under modern immunosuppression. American Journal of Transplantation, 5, 2740-44. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/16212635>.

- Risk factors for acute rejection with early corticosteroid withdrawal within 7 days included African American race, DGF, any number of HLA mismatches, PRA > 25%, re-transplantation, Thymoglobulin induction, type 1 diabetes, and deceased donor kidney transplantation.

Woodle, ES et al. (2008). A prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 days) corticosteroid cessation versus long-term, low-dose corticosteroid therapy. Annals of Surgery, 248, 564-77. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/18936569>.

- Non-highly sensitized kidney transplant recipients (PRA < 25%, first transplant, non-DGF) were randomized to receive prednisone or early corticosteroid withdrawal at seven days post-transplant. While there were improvements in cardiovascular outcomes and similar long-term graft

survival and function, early corticosteroid withdrawal was associated with an increased risk of rejection episodes.

Xie X, Jiang Y, Lai X, Xiang S, Shou Z, Chen J. mTOR inhibitor versus mycophenolic acid as the primary immunosuppression regime combined with calcineurin inhibitor for kidney transplant recipients: a meta-analysis. *BMC Nephrol*. 2015;16:91. Retrieved from:
<https://www.ncbi.nlm.nih.gov/pubmed/26126806>

- Review of 11 randomized controlled trials (n=4930 patients) comparing mTOR to MPA as the primary immunosuppressive regimen in combination with CNI. No significant difference in risk of biopsy-proven acute rejection and patient death between the two groups. However, the mTOR group had increased risk of graft loss and inferior graft function compared to MPA. Patients treated with mTOR had a higher risk of new-onset diabetes mellitus, dyslipidemia, proteinuria, peripheral edema, and thrombocytopenia. MPA group had higher risk of cytomegalovirus infection, malignancy, and leucopenia.

1.3. Desensitization therapy

Akalin E, et al. (2008). Addition of plasmapheresis decreases the incidence of acute antibody-mediated rejection in sensitized patients with strong donor-specific antibodies. *Clinical Journal of the American Society of Nephrology*, 2008, 3, 1160-7. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/18337549>.

- In CDC and/or flow cytometry crossmatch positive kidney transplant recipients receiving induction of thymoglobulin 1.5 mg/kg daily for five days plus high-dose IVIG (1 g/kg during transplant and 500 mg/kg POD 1 and 2), 66% of those with strong (MFI > 6000) DSA had acute rejection

whereas 0% of those with weak-moderate (>1500-5999) DSA had acute rejection

- Subsequently, recipients with strong DSA also received peri-transplant plasmapheresis (4-8 sessions prior to transplant) until DSA reduced to weak-moderate, resulting in reduction of acute rejection to 7%

Bentall A, et al. (2013). Five-year outcomes in living donor kidney transplants with a positive crossmatch. *American Journal of Transplantation*, 13 (1), 76-85. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/23072543>.

- Actual 5-year death-censored graft survival was lower in positive crossmatch kidney transplant recipients versus negative crossmatch kidney transplant recipients (70.7% vs. 88.0%, p<0.01); transplant glomerulopathy was present in 54.5% of surviving grafts
- Graft survival was higher in recipients with antibody against donor class I only compared to antibody against class II, alone or in combination with class I (85.3% vs. 62.6%, p=0.05)

Burns JM, et al. (2008). Alloantibody levels and acute humoral rejection early after positive crossmatch kidney transplantation. *American Journal of Transplantation*, 8, 2684-94.

Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/18976305>.

- AMR occurs at a wide spectrum of baseline DSA as determined by T- and B-cell flow cytometry crossmatch levels, including those associated with a negative T-cell AHG crossmatch
- Risk of AMR generally increases with increasing baseline DSA, but is unpredictable

Diwan TS, et al. (2011) The impact of proteasome inhibition on alloantibody-producing plasma cells in vivo. *Transplantation*, 91, 536-41. Retrieved from
<http://www.ncbi.nlm.nih.gov/pubmed/21283064>.

- Eight highly-sensitized living-donor kidney transplant recipients with a B-cell flow cytometry crossmatch >450 receiving four or sixteen doses of bortezomib 1.3 mg/m²/dose alone resulted in significant depletion of DSA producing plasma cells (16.7 ± 14.5 cells/mL before vs. 6.2 ± 3.6 cells/mL after, p=0.048), but did not decrease DSA levels

Glotz D, et al. (2002). Desensitization and subsequent kidney transplantation of patients using intravenous immunoglobulins (IVIG). *American Journal of Transplantation*, 2002, 2, 758-60. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12243496>.

- Desensitization with 3 monthly courses of IVIG 2 g/kg resulted in a transplantation rate of 87% (13/15)
- One graft was lost due to thrombosis and one due to rejection at one year follow up

Huber L, et al. (2012) Identification and therapeutic management of highly sensitized patients undergoing renal transplantation. *Drugs*, 72, 1335-54. Retrieved from
<http://www.ncbi.nlm.nih.gov/pubmed/22747448>.

- A thorough review regarding the management of highly sensitized patients undergoing renal transplantation

Jeong JC, Jambaldorj E, Kwon HY, et al. Desensitization Using Bortezomib and High-dose Immunoglobulin Increases Rate of Deceased Donor Kidney Transplantation. *Medicine* (Baltimore). 2016;95(5):e2635. Retrieved from:
<https://www.ncbi.nlm.nih.gov/pubmed/26844479>

- Prospective, open-labeled clinical trial of 36 patients comparing rate of DDRT between sensitized patients; IVIG (2 g/kg x 2 doses), rituximab (375 mg/m² x 1 dose), bortezomib (1.3 mg/m² x 4 doses) vs. control. Multivariate time-varying covariate Cox regression analysis showed that desensitization increased the probability of DDRT (hazard ratio, 46.895; 95% confidence interval, 3.468–634.132; P=0.004). Desensitization was well tolerated, and acute rejection occurred only in the control group.

Jordan SC, et al. (2004). Evaluation of intravenous immunoglobulin as an agent to lower allosensitization and improve transplantation in highly sensitized adult patients with end-stage renal disease: report of the NIH IGO2 trial. *Journal of American Society of Nephrology*, 15, 3256-62. Retrieved from

<http://www.ncbi.nlm.nih.gov/pubmed/15579530>.

- IVIG 2 g/kg monthly for 4 months significantly reduces PRA levels after one year
- More patients who received IVIG were transplanted and subsequently developed rejection as compared to those receiving placebo

Lefaucheur C, et al (2010). Preexisting donor-specific HLA antibodies predict outcome in kidney transplantation. *Journal of American Society of Nephrology*, 21, 1398-406.

Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/20634297>.

- 8-year graft survival significantly worse (61%) among patients with pre-existing HLA-DSA compared with both sensitized patients without HLA-DSA (93%) and non-sensitized patients (84%)
- Patients with MFI >6000 had >100-fold higher risk for AMR than patients with MFI <465

Lemy A, et al (2010). Bortezomib: a new player in pre- and post-transplant desensitization? *Nephrology Dialysis Transplantation*, 25, 3480-9. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/20826741>.

- Review of the use of bortezomib as part of a desensitization protocol

Marfo K, et al (2011). Desensitization protocols and their outcome. *Clinical Journal of the American Society of Nephrology*, 6, 922-936. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/21441131>.

- In-depth review of desensitization treatment modalities and clinical outcomes of various protocols

Montgomery RA (2010). Renal transplantation across HLA and ABO antibody barriers: integrating paired donation into desensitization protocols. *American Journal of Transplantation*, 10, 449-57. Retrieved from

<http://www.ncbi.nlm.nih.gov/pubmed/20121749>.

- Review of kidney transplantation options for sensitized patients by integrating paired donation with desensitization protocols

Montgomery RA, et al. (2011). Desensitization in HLA-incompatible kidney recipients and survival. *New England Journal of Medicine*, 365, 318-26. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/21793744>.

- 8-year Kaplan-Meier estimates of patient survival greater for desensitization treatment vs. dialysis-only and dialysis-or-transplantation (80.6% vs. 30.5% or 49.1%, p<0.001)

Stegall MD, et al. (2006). A comparison of plasmapheresis versus high-dose IVIG desensitization in renal allograft recipients with high levels of donor specific alloantibody. *American Journal of Transplantation*, 6, 346-51. Retrieved from

<http://www.ncbi.nlm.nih.gov/pubmed/16426319>.

- A negative crossmatch was achieved in 38% of patients receiving high-dose IVIG, 84% of patients receiving low-dose IVIG, plasmapheresis, and rituximab, and 88% of patients receiving low dose IVIG, plasmapheresis, rituximab, and pre-transplant Thymoglobulin combined with post-transplant DSA monitoring
- Even with a negative crossmatch, rejection rates were 80% vs. 37% vs. 29%, respectively ($p<0.05$, high-dose IVIG vs. low-dose IVIG, plasmapheresis, and rituximab)
- Multiple plasmapheresis treatment sessions leads to more reproducible desensitization and lower rates of AMR

Stegall MD, et al. (2011). Terminal complement inhibition decreases antibody-mediated rejection in sensitized renal transplant recipients. American Journal of Transplantation, 11, 2405-13. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/21942930>.

- Eculizumab (1200 mg POD 0, 600 mg POD 1, and then 600 mg weekly for 4+ weeks) used for prevention of AMR in positive crossmatch living-donor kidney transplant recipients resulted in AMR in 7.7% at 3 months vs. 41.2% among historical controls
- One-year protocol biopsy showed transplant glomerulopathy in 6.7% of eculizumab-treated recipients vs. 35.7% of control patients ($p=0.044$)

Vo AA, Choi J, Cisneros K, et al. Benefits of rituximab combined with intravenous immunoglobulin for desensitization in kidney transplant recipients. Transplantation. 2014;98(3):312-9. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/24770617>

- Renal transplant recipients ($n=13$) were randomized to IVIG + placebo versus IVIG + rituximab. No significant differences were seen in DSA levels at

transplant. ABMR episodes and DSA rebound occurred in the IVIG+placebo group 43% vs 0% in IVIG+ rituximab group, P=0.06. Renal function at 6 and 12 months showed a significant benefit for IVIG+rituximab, P=0.04. IVIG+rituximab appeared more effective in preventing DSA rebound, ABMR and development of transplant glomerulopathy.

Vo AA, et al. (2008). Rituximab and intravenous immune globulin for desensitization during renal transplantation. New England Journal of Medicine, 359, 242-51. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/18635429>.

- Desensitization with high-dose IVIG 2 g/kg on days 0 and 30 plus rituximab 1 g on days 7 and 22 resulted in significant reduction of mean panel reactive antibody ($77 \pm 19\%$ before to $44 \pm 30\%$ after, p<0.001)
- 16 of 20 (80%) patient received a transplant and patient and graft survival at 12 months were 100% and 94%, respectively

Vo AA, et al. (2013). Efficacy, outcomes, and cost-effectiveness of desensitization using IVIG and rituximab. Transplantation, 95(6), 852-8. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/23511212>.

- 71% of sensitized patients were transplanted using the desensitization protocol of IVIG 2 g/kg x 2 doses plus rituximab 1 g
- Each transplanted patient saved the U.S. healthcare system an estimated \$18,753 as compared to remaining on dialysis

1.4. Management of rejection

Alarcon-zurita A, Ladefoged J. Treatment of acute allograft rejection with high doses of corticosteroids. Kidney Int. 1976;9(4):351-4. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/781384>

- 55 kidney transplant patients were treated with high doses of corticosteroids, either prednisone (oral 150 – 600mg/day); methylprednisolone (IV 0.5 to 1g/day [total dose: 2 to 8 g]); methylprednisone (same dose + heparin 5000 U/day). Acute rejection was reversed in 60% of patients without any difference between the three treatment groups. Nineteen patients died from steroid-related complications. Authors suggest that total methylprednisolone dosage exceeding 3 to 5 g did not lead to significant improvement and therefore does not warrant the additional risk.

Becker YT, et al. (2004). Rituximab as treatment for refractory kidney transplant rejection. American Journal of Transplantation, 2004, 996-1001. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/15147435>.

- Kidney transplant recipients diagnosed with steroid-resistant BPAR given rituximab (375 mg/m²) and methylprednisolone +/- plasmapheresis and thymoglobulin resulted in graft loss in only 3/27
- In the 24 successfully treated recipients, serum creatinine declined from 5.6 ± 1.0 to 0.95 ± 0.7 at discharge

Cooper JE, Gralla J, Klem P, Chan L, Wiseman AC. High dose intravenous immunoglobulin therapy for donor-specific antibodies in kidney transplant recipients with acute and chronic graft dysfunction. Transplantation. 2014;97(12):1253-9. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/24937199>

- Retrospective analysis of 28 kidney transplant recipients with de novo DSA and graft damage (chronic graft dysfunction or AMR) given standard regimen of high-dose (5 g/kg) IVIG dosed over 6 months. High-dose IVIG resulted in modest DSA MFI reductions in patients with previous graft damage, mostly

class I DSA in patients with AMR. There was no clinical benefit in patients with chronic graft damage, whereas high-dose IVIG may reduce the risk of chronic graft dysfunction in those with an acute AMR event.

Colvin RB, et al. (2007). Antibody-mediated renal allograft rejection: diagnosis and pathogenesis. *Journal of American Society of Nephrology*, 18, 1046-56. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/17360947>.

- Review of the diagnosis and pathogenesis of acute and chronic AMR
Eskandary F, Bond G, Schwaiger E, et al. Bortezomib in late antibody-mediated kidney transplant rejection (BORTEJECT Study): study protocol for a randomized controlled trial. *Trials*. 2014;15:107. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/24708575>
- Single center study of intravenous bortezomib on the course of late AMR
randomized 44 patients to two cycles of bortezomib ($4 \times 1.3 \text{ mg/m}^2$ over 2 weeks; 3-month interval between cycles) vs. placebo. Primary end point will be the course of eGFR over 24 months. Secondary endpoints will be DSA levels, protein excretion, measured glomerular filtration rate, transplant and patient survival, and the development of acute and chronic morphological lesions in 24-month protocol biopsies.
- Results: To be determined (24 month follow-up study)

Everly M, et al. (2008). Bortezomib provides effective therapy for antibody- and cell-mediated acute rejection. *Transplantation*, 86, 1754-61. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/19104417>.

- Case series of 6 patients with concomitant AMR and ACR, refractory to with plasmapheresis \pm IVIG \pm rATG \pm methylprednisolone \pm rituximab, received addition of bortezomib therapy (1.3 mg/m² for four doses)

- Bortezomib therapy provided resolution of refractory ACR, marked and sustained reduction in DSA within 2-4 weeks, regardless of initial DSA level, improved renal function, and suppression of recurrent rejection for at least 5 months

Flechner SM, et al. (2010). the role of proteasome inhibition with bortezomib in the treatment of antibody-mediated rejection after kidney-only or kidney-combined organ transplantation. *Transplantation*, 90, 1486-92. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/21042239>.

- Case series of 20 kidney transplant recipients with AMR who received rescue therapy with IV corticosteroids followed by a 2-week cycle of plasmapheresis on days 1, 4, 8, and 11, and bortezomib 1.3 mg/m², then IVIG 0.5 mg/kg for four doses
- Patients had substantial reduction in DSA, but only 10% had undetectable DSA after treatment
- Each treated patient had an initial improvement in serum creatinine, but only 25% returned to baseline renal function

Gaber AO, et al. (1998). Results of the double-blind, randomized, multicenter, phase III clinical trial of thymoglobulin versus Atgam in the treatment of acute graft rejection episodes after renal transplantation. *Transplantation*, 66(1), 29-37. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9679818>.

- Thymoglobulin was superior to Atgam in reversing acute rejection (88% vs. 76%, p=0.027) and preventing recurrent rejection (17% vs. 36%, p=0.011)

Jordan SC, et al. (2005). Post-transplant therapy with high-dose intravenous gammaglobulin: Applications to treatment of antibody-mediated rejection. *Pediatric*

Transplantation, 9, 155-61. Retrieved from

[http://www.ncbi.nlm.nih.gov/pubmed/15787786.](http://www.ncbi.nlm.nih.gov/pubmed/15787786)

- Review of AMR and experience of high-dose IVIG at Cedars-Sinai Medical Center

Jordan SC, et al. (2011). Clinical aspects of intravenous immunoglobulin use in solid organ transplant recipients. American Journal of Transplantation, 2011, 11, 196-202. Retrieved from [http://www.ncbi.nlm.nih.gov/pubmed/21219579.](http://www.ncbi.nlm.nih.gov/pubmed/21219579)

- Review of the clinical application of IVIG in solid organ transplant recipients

Joudeh A, et al (2013). Pathologic basis of antibody-mediated organ transplant rejection: from pathogenesis to diagnosis. Current Opinion in Organ Transplantation, 18(4), 478-85. Retrieved from [http://www.ncbi.nlm.nih.gov/pubmed/23838653.](http://www.ncbi.nlm.nih.gov/pubmed/23838653)

- Review of the diagnosis and pathogenesis of acute and chronic AMR

KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients (2009). Chapter 6: treatment of acute rejection. American Journal of Transplantation, 9 (suppl 3), S21-S22. Retrieved from

[http://www.kdigo.org/pdf/KDIGO%20Txp%20GL%20publ%20version.pdf.](http://www.kdigo.org/pdf/KDIGO%20Txp%20GL%20publ%20version.pdf)

- Evidence-based recommendations for the treatment of acute rejection

Kim M, Martin ST, Townsend KR, Gabardi S. Antibody-mediated rejection in kidney transplantation: a review of pathophysiology, diagnosis, and treatment options.

Pharmacotherapy. 2014;34(7):733-44. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pubmed/24753207>

- Review of the standard of care for AMR, including; plasmapheresis, intravenous immunoglobulin, rituximab and alemtuzumab, bortezomib, and eculizumab

Kocak B, Arpalı E, Demiralp E, et al. Eculizumab for salvage treatment of refractory antibody-mediated rejection in kidney transplant patients: case reports. *Transplant Proc.* 2013;45(3):1022-5. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/23622614>

- Review of 2 patient cases of acute-onset AMR in preoperatively desensitized patients treated with Eculizumab

Kurtkoti J, et al. (2008). The utility of 1- and 3-month protocol biopsies on renal allograft function: a randomized controlled study. *American Journal of Transplantation*, 8, 317-23. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/18093273>.

- Graft function (serum creatinine and MDRD eGFR) was superior at 6 months and 1 year amongst patients who underwent protocol biopsies, but no difference in the incidence of clinical acute rejection

Lefaucheur C, et al. (2009). Comparison of combination Plasmapheresis/IVIg/anti-CD20 versus high-dose IVIg in the treatment of antibody-mediated rejection. *American Journal of Transplantation*, 9, 1099-107. Retrieved from

<http://www.ncbi.nlm.nih.gov/pubmed/19422335>.

- Kidney transplant recipients with AMR treated with either (Group A) high-dose IVIG (2 g/kg over 2 days every 3 weeks for 4 doses) or (Group B) plasmapheresis (4 sessions) plus low-dose IVIG (100 mg/kg after plasmapheresis) plus high-dose IVIG (2 g/kg over 2 days every 3 weeks for 4 doses) and rituximab (375 mg/m² once weekly for two weeks) after the last plasmapheresis
- Graft survival at 36 months was 91.7% with combination therapy (Group B) vs. 50% with high-dose IVIG alone (Group A) (p=0.02)

Lehrich RW, Rocha PN, Reinsmoen N, et al. Intravenous immunoglobulin and plasmapheresis in acute humoral rejection: experience in renal allograft transplantation.

Hum Immunol. 2005;66(4):350-8. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pubmed/15866697>

- Retrospective review classifying patients according to biopsy results into three groups: AHR, (n=23) ACR (n=75), and no rejection. AHR was treated with IVIG and PP resulting in similar IVIG graft survival to patients with ACR.

Levine MH, et al. (2012). Treatment options and strategies for antibody mediated rejection after renal transplantation. Seminars in Immunology, 24, 136-42. Retrieved from

<http://www.ncbi.nlm.nih.gov/pubmed/21940179>.

- In-depth review of AMR and treatment modalities

Mengel M, et al. (2012). Banff 2011 meeting report: new concepts in antibody-mediated rejection. American Journal of Transplantation, 12, 563-70. Retrieved from

<http://www.ncbi.nlm.nih.gov/pubmed/22300494>.

- Updates from the 2011 Banff meeting, with a focus on refining criteria for AMR

Montgomery RA, Zachary AA, Racusen LC, et al. Plasmapheresis and intravenous immune globulin provides effective rescue therapy for refractory humoral rejection and allows kidneys to be successfully transplanted into cross-match-positive recipients.

Transplantation. 2000;70(6):887-95. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pubmed/11014642>

- Live donor kidney transplant recipients (n=7) who experienced AHR and had donor-specific Ab (DSA) were segregated into two groups: treated for established AHR (rescue group, n=3) and received therapy before transplantation (preemptive group, n=4). Using PP/IVIG we have successfully reversed established AHR in three patients. Combined therapies of PP/IVIG

were successful in reversing AHR mediated by Ab specific for donor HLA antigens.

Mulley, et al. (2011). Understanding crossmatch testing in organ transplantation: a case-based guide for the general nephrologist. *Nephrology*, 16, 125-33. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/21272123>.

- Case-based guide of the various crossmatching techniques

Nankivell BJ, et al. (2010). Rejection of the kidney allograft. *New England Journal of Medicine*, 363, 1451-62. Retrieved from

<http://www.ncbi.nlm.nih.gov/pubmed/20925547>.

- Review of the mechanisms and clinical features of cellular and antibody mediated rejection

Puttarajappa C, et al. (2012). Antibody-mediated rejection in kidney transplantation: a review. *Journal of Transplantation*, 193724. Retrieved from

<http://www.ncbi.nlm.nih.gov/pubmed/22577514>.

- Review of histopathological and clinical manifestations of AMR, as well as treatment modalities

Raghavan R, Jeroudi A, Achkar K, Gaber AO, Patel SJ, Abdellatif A. Bortezomib in kidney transplantation. *J Transplant*. 2010. Retrieved from:

<https://www.ncbi.nlm.nih.gov/pubmed/20953363>

- Literature review of bortezomib for desensitization and treatment of AMR

Roberts DM, et al. (2012). The treatment of acute antibody-mediated rejection in kidney transplant recipients-a systematic review. *Transplantation*, 94, 775-83. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/23032865>.

- Systematic review of heterogeneous studies examining the treatment of acute AMR

Rush D, et al. (1998). Beneficial effects of treatment of early subclinical rejection: a randomized study. *Journal of American Society of Nephrology*, 9, 2129-34. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9808101>.

- Corticosteroid treatment of early subclinical rejection is associated with a decrease in early (month 2 and 3) and late (months 7 to 12) clinical rejection, a decrease in chronic tubulointerstitial score at 6 months, and a lower serum creatinine at 24 months

Sautenet B, Blancho G, Büchler M, et al. One-year Results of the Effects of Rituximab on Acute Antibody-Mediated Rejection in Renal Transplantation: RITUX ERAH, a Multicenter Double-blind Randomized Placebo-controlled Trial. *Transplantation*. 2016;100(2):391-9. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/26555944>

- Multicenter, double-blind, placebo-controlled trial, randomized 38 patients with biopsy proven AMR to receive rituximab (375 mg/m²) or placebo at day 5. All patients received PE, IVIg, and CS. Primary endpoint (composite of graft loss or no improvement in renal function at day 12) frequency was similar in both groups. Both groups showed improved histological features of AMR and decreased mean fluorescence intensity of donor-specific antibodies. This study was underpowered, but concluded that rituximab had no additional benefit in patients for AMR.

Shah A, Nadasdy T, Arend L, et al. Treatment of C4d-positive acute humoral rejection with plasmapheresis and rabbit polyclonal antithymocyte globulin. *Transplantation*. 2004;77(9):1399-405. Retrieved from: <https://www.ncbi.nlm.nih.gov/pubmed/15167598>

- Case series of 7 patients with AMR treated with PPH (mean of 6.8 treatments) in combination with rATG (0.75 mg/kg/day 5–10 days) until the serum creatinine returned to 120% of nadir. For 6 patients, nadir

posttreatment creatinine was significantly lower than pretreatment creatinine ($P<0.007$) with only one episode of graft loss. Combination therapy using PPH and rATG is an effective means of reversing AHR in renal allograft

Sis B, et al. (2010). Banff '09 meeting report: antibody mediated graft deterioration and implementation of Banff working groups. American Journal of Transplantation, 10, 464-71.

Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/20121738>.

- Updates from the 2009 Banff meeting, with a focus on alloantibody responses, roles of endothelial cells in rejection, non-invasive markers of rejection, and updates on kidney, pancreas, heart, liver, lung, and composite tissue graft pathology

Solez K, et al.(2007). Banff '05 meeting report: differential diagnosis of chronic allograft injury and elimination of chronic allograft nephropathy ('CAN'). American Journal of Transplantation, 7, 518-26. Retrieved from

<http://www.ncbi.nlm.nih.gov/pubmed/17352710>.

- Updates from the 2005 Banff meeting, with a major topic of discussion being the elimination of the term "chronic allograft nephropathy" from the Banff schema for diagnosis and grading of renal allograft rejection

Solez K, et al (2008). Banff 07 classification of renal allograft pathology: updates and future directions. American Journal of Transplantation, 8, 753-60. Retrieved from

<http://www.ncbi.nlm.nih.gov/pubmed/18294345>.

- Updates from the 2007 Banff meeting, with a focus on PTC grading, C4d scoring, interpretation of C4d deposition without morphological evidence of active rejection, application of the Banff criteria to zero-time and protocol

biopsies, and introduction of a new scoring for total interstitial inflammation (ti-score)

van den Hoogen MW, et al. (2013). Treatment of steroid-resistant acute renal allograft rejection with alemtuzumab. *American Journal of Transplantation*, 13, 192-6. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/23167538>.

- Comparison of steroid-resistant kidney rejection of patients treated with alemtuzumab (15-30 mg subcutaneously on two subsequent days) vs. previous patients treated with rATG (2.5-4.0 mg/kg IV for 10-14 days), in which similar incidence of treatment failure was observed (27% vs. 40%, p=0.70)
- More infusion-related side-effects were observed in rATG treated patients (27% vs. 85%, p=0.013)

Waiser J, et al. (2012). Comparison between bortezomib and rituximab in the treatment of antibody-mediated renal allograft rejection. *Nephrology Dialysis Transplantation*, 27, 1246-51. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/21852274>.

- Kidney transplant recipients with AMR treated with bortezomib (1.3 mg/m² x 4 doses) compared to historical patients treated with rituximab (500 mg x 1 dose); all recipients treated with plasmapheresis (6 sessions) and IVIG 30 g after last plasmapheresis
- 9 months after treatment renal function was superior in the bortezomib group (SCr: 2.5 ± 0.6 vs. 5.1 ± 2.1, p=0.0008)
- 18 months after treatment, graft survival was superior in the bortezomib group (6/10 vs. 1/9, p=0.071)

Walsh RC, et al. (2010). Proteasome inhibitor-based primary therapy for antibody-mediated renal allograft rejection. *Transplantation*, 89(3), 277-84. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/20145517>.

- Two case reports showing bortezomib as a potential means for rapid DSA elimination in early acute AMR

Walsh RC, et al. (2011). Early and late acute antibody-mediated rejection differ immunologically and in response to proteasome inhibition. *Transplantation*, 91, 1218-26. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/21617586>.

- Kidney transplant recipients treated with a combination of bortezomib (1.3 mg/m² x 4 doses), rituximab (375 mg/m² before the first bortezomib dose), and plasmapheresis (before each bortezomib dose) for AMR +/- ACR
- Recipients with early AMR (< 6 months post-transplant) demonstrated a lower DSA nadir compared to those with late AMR (> 6 months post-transplant) ($81.5\% \pm 21.2\%$ vs. $51.4\% \pm 27.6\%$, p<0.01) and were more likely to have histologic resolution/improvement (87.5% vs. 53.8%, p=0.13)

Webster AC, et al. (2006). Monoclonal and polyclonal antibody therapy for treating acute rejection in kidney transplant recipients: a systemic review of randomized trial data. *Transplantation*, 81(7), 953-65. Retrieved from

<http://www.ncbi.nlm.nih.gov/pubmed/16612264>.

- Comprehensive systematic review of trials utilizing monoclonal antibody (muromonab-CD3) and polyclonal antibody (ATG, ALG) therapies to treat acute rejection in kidney transplant recipients

Zarkhin V, et al. (2008). A randomized, prospective trial of rituximab for acute rejection in pediatric renal transplantation. *American Journal of Transplantation*, 8, 2607-17.

Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/18808404>.

- Prospective study of pediatric kidney transplant recipients with acute rejection (BPAR and > 1 B-cell-infiltrating clusters with absolute count > 100 CD20+ cells/hpf) treated with standard therapy of pulsed steroid +/- thymoglobulin (1.5 mg/kg/dose x 6 doses) +/- the addition of rituximab (375 mg/m² weekly for 4 weeks)
- Rituximab treated recipients showed a higher trend in creatinine clearance (p=0.026) and showed significant improvement in 1-month follow up biopsy scores (p=0.0003)

1.5. Retransplant/graft failure

Ahmed, K et al. (2008). Influence of number of retransplants on renal graft outcome.

Transplantation Proceedings, 40, 1349–52. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/18589103>.

- Single-center, retrospective analysis of graft outcomes amongst patients with a history of multiple (>2) kidney transplants compared to a cohort of patients receiving their first graft during the same period. Graft survival rates were not different among patients with a history of two compared to more than two transplants; the authors suggest that kidney retransplantation can yield acceptable graft survival rates, albeit significantly lower than primary transplantation.

Magee, JC et al. (2007). Repeat organ transplantation in the United States, 1996–2005.

American Journal of Transplantation, 7: 1424–33. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/17428290>.

- Compared to other organ types, the number of repeat kidney transplants has grown most significantly over the past 10 years (absolute increase 40%, represented 12.4% of all kidney transplants in 2005). However, graft survival rates at 1-, 3-, and 5 years following retransplantation are significantly lower than those observed for primary transplants.

Marcen, R et al. (2008). Patient outcomes after kidney allograft loss. Transplantation

Reviews, 22, 62-72. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/18631859>.

- Review article of kidney graft failure, including considerations for the management of patients after graft loss, patient outcomes, and retransplantation.

Meier-Kriesche, HU et al. (2004). Lack of improvement in renal allograft survival despite a

marked decrease in acute rejection rates over the most recent era. American Journal of

Transplantation, 4, 378-83. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/14961990>.

- Analysis of Scientific Registry of Transplant Recipients (SRTR) data of all adult first renal transplants between 1995 and 2000. While the authors noted a decrease in acute rejection rates post-transplant (6-months, 12-months, and late rejections), there was no significant improvement in overall graft survival.

Miles, CD et al. (2007). Mortality experience in recipients undergoing repeat

transplantation with expanded criteria donor and non-ECD deceased-donor kidneys.

American Journal of Transplantation, 7, 1140-47. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/17331109>.

- Data from the Scientific Registry of Transplant Recipients (SRTR) of all adult kidney transplant recipients who experienced graft failure and were relisted for transplantation between 1995 and 2004. While a survival benefit was observed with non-ECD kidneys, retransplantation with ECD kidneys did not offer a significant survival benefit over remaining on dialysis.

Ojo, A et al. (1998). Prognosis after primary renal transplant failure and the beneficial effects of repeat transplantation: multivariate analyses from the United States Renal Data System. *Transplantation*, 27, 1651-59. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/9884254>.

- United States Renal Data System (USRDS) data evaluating survival outcomes of 19,208 kidney transplant recipients who experienced primary graft loss between 1985 and 1995, as evidenced by return to maintenance dialysis, wait-listing for repeat transplantation, or receipt of a second kidney transplant. Repeat transplantation was associated with a substantial improvement in 5-year mortality rates.

1.6. Kidney diseases

1.6.1. Glomerular disease

Chadban, SJ et al. (2005). Glomerulonephritis. *The Lancet*, 365, 1797-806. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/15910953>.

- Review article of the epidemiology, pathophysiology, and initial management of various types of glomerular diseases.

Hricik, DE et al. (1998). Glomerulonephritis. New England Journal of Medicine, 24, 888-99. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/9744974>.

- Review article of the pathophysiology and clinical presentation of acute, rapidly progressing, and chronic glomerulonephritis.

KDIGO Clinical Practice Guideline for Glomerulonephritis. (2012). Volume 2, Issue 2.

Retrieved from http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO-GN-Guideline.pdf

- Therapeutic guidelines containing chapters on various glomerular diseases (lupus nephritis, membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis, infection-related glomerulonephritis, IgA nephropathy, etc) and recommended treatment approaches.

Focal Segmental Glomerulosclerosis

Burgess, E et al. (1999). Management of focal segmental glomerulosclerosis: Evidence-based recommendations. Kidney International, 70, S26-32. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/10369192>.

- Graded recommendations developed by the International Society of Nephrology for the treatment of FSGS. Steroids are the first-line treatment approach, with resistance being declared only if patients do not achieve remission after a six-month trial; second-line options include cyclosporine, cytotoxic therapy (cyclophosphamide, azathioprine, chlorambucil), and plasmapheresis for kidney transplant recipients with recurrent FSGS.

D'Agati, VD et al. (2011). Focal segmental glomerulosclerosis. New England Journal of Medicine, 365, 2398-411. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/22187987>.

- Review article of the pathophysiology, clinical presentation, therapeutic options, and treatment algorithm for focal segmental glomerulosclerosis. The article concludes with considerations of disease recurrence following renal transplantation.

Fernandez-Fresnedo, G et al. (2009). Rituximab treatment of adult patients with steroid-resistant focal segmental glomerulosclerosis. Clinical Journal of the American Society of Nephrology, 4, 1317-23. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/19578004>.

- Eight patients with biopsy-proven FSGS and had received rituximab (375 mg/m² weekly x 4) for disease resistant to corticosteroids and other therapies (including cyclosporine, tacrolimus, mycophenolate, cyclophosphamide, chlorambucil) were included. At the end of follow-up, patients experienced a modest reduction in proteinuria (14.0 vs. 10.5 g/24h) but serum creatinine increased and only two patients achieved a remarkable and sustained reduction in proteinuria.

Ochi, A et al. (2012). Rituximab treatment for adult patients with focal segmental glomerulosclerosis. Internal Medicine, 51, 759-796. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/22466834>.

- Case series of single-dose rituximab administration in the setting of steroid-resistant (n=2) and steroid-dependent FSGS (n=2). Patients with steroid-dependent FSGS responded to rituximab therapy while those with steroid-resistant FSGS did not.

Lupus Nephritis

Appel, GB et al. (2009). Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *Journal of the American Society of Nephrology*, 20, 1103-12. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/19369404>.

- Patients with biopsy-proven lupus nephritis were randomized to treatment with mycophenolate mofetil (target dose 1.5 g oral BID) or cyclophosphamide (0.5 - 1 g/m² monthly) in combination with oral steroids. Mycophenolate was non-inferior to cyclophosphamide in terms of reduction in urine protein:creatinine ratio, change in serum creatinine, or tolerability. Mycophenolate allows for convenient oral dosing and eliminates the risk of ovarian dysfunction associated with cyclophosphamide.

Dooley, MA t al. (2011). Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. *New England Journal of Medicine*, 365, 1886-1895. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/22087680>.

- Patients with active class III, IV, or V lupus nephritis were randomized to maintenance therapy with mycophenolate (1 g oral BID) or azathioprine (2 g/kg/day) in combination with corticosteroids (10 mg of prednisone per day or less). Mycophenolate was superior to azathioprine with respect to time to treatment failure (defined by renal flare, end-stage renal disease, doubling of the serum creatinine, or need for rescue therapy).

Hahn, BH et al. (2012). American College of Rheumatology (ACR) guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care and Research*, 64, 797-808. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/22556106>.

- Guidelines and recommendations developed by the American College of Rheumatology to provide guidance to physicians managing patients with lupus nephritis.

Roving, BH et al. (2012). Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis and Rheumatism, 64, 1215-26. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/22231479>.

- Patients with lupus nephritis were randomized to receive placebo or rituximab (1 g IV on days 1, 15, 168, and 182) in addition to mycophenolate mofetil and corticosteroids. Although rituximab resulted in significant improvements in C3, C4, and anti-dsDNA levels and higher response rates (46% vs. 57%, p=0.18), clinical outcomes at one year were similar. In an underpowered subgroup analysis, African American patients achieved better outcomes with rituximab.

Membranous Glomerulonephritis

Waldman, M et al. (2012). Treatment of idiopathic membranous nephropathy. Journal of the American Society of Nephrology, 23, 1617-30. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/22859855>.

- Review article of the pathophysiology, pharmacologic options, and current approach to treatment for idiopathic membranous nephropathy.

Ruggenenti, P et al. (2012). Rituximab in idiopathic membranous nephropathy. Journal of the American Society of Nephrology, 23, 1416-25. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/22822077>.

- Outcomes following rituximab administration (375 mg/m² weekly x 4) in the setting of idiopathic membranous nephropathy with persistent

proteinuria. During a median follow-up of 29 months, 65 of 100 patients achieved complete (<0.3 g/day) or partial remission (<3 g/day) at a median of 7.1 months after administration, while 4 patients progressed to ESRD. The magnitude of proteinuria significantly correlated with a slower decline in eGFR.

IgA Nephropathy

Wyatt, RJ et al. (2013). IgA nephropathy. New England Journal of Medicine, 368, 2402-14. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/23782179>.

- Review article of the pathophysiology, clinical outcomes, and treatment options for IgA nephropathy. IgA nephropathy is considered a glomerular disease as well as autoimmune disease.

Post-Infectious Glomerulonephritis

Rodriguez-Iturbe, B et al. (2008). The current state of poststreptococcal glomerulonephritis. Journal of the American Society of Nephrology, 19, 1855-64.

Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/18667731>.

- Post-streptococcal glomerulonephritis is becoming increasingly rare in industrialized countries, though the incidence in developing nations remains high and prophylactic antibiotic treatment in endemic regions may be warranted. Genome sequencing may allow for recognition of strains likely to cause disease and improved clinical research.

Membranoproliferative Glomerulonephritis

Sethi, S et al. (2012). Membranoproliferative glomerulonephritis – a new look at an old entity. New England Journal of Medicine, 366, 1119-31. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/22435371>.

- Review article of membranoproliferative glomerulonephritis, including the pathophysiology, disease types (complement-mediated, immune complex-mediated), clinical presentation, and therapeutic management. The underlying process should be identified in order to facilitate appropriate disease management.

1.6.2. Hypertensive nephrosclerosis

Appel, LR et al. (2010). Intensive blood pressure control in hypertensive chronic kidney disease. *New England Journal of Medicine*, 363, 918-29. Retrieve from:
<http://www.ncbi.nlm.nih.gov/pubmed/20818902>.

- African American patients with hypertensive chronic kidney disease were randomized to receive intensive (<130/80mmHg) or standard (<140/90mmHg) blood pressure control in order to evaluate whether blood pressure control can slow the progression of renal disease. Intensive blood pressure control had no effect on kidney disease progression, though patients with baseline proteinuria demonstrated a potential benefit.

Caetano, ER et al. (2001). Hypertensive nephrosclerosis as a relevant cause of chronic renal failure. *Hypertension*, 38, 171-76. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/11509471>.

- Study evaluating renal biopsies of hypertensive patients (SBP >160 mmHg and/or DBP >95 mmHg) with moderate renal insufficiency (SCr > 1.5 mg/dL) with no clinical evidence of primary or ischemic renal disease. While hypertension alone contributed to benign and malignant nephrosclerosis, a significant fraction of patients with an initial clinical diagnosis of hypertensive nephrosclerosis were found to have histological evidence of primary renal disease (i.e. FSGS).

Freedman, BI et al. (2008). Hypertension-associated kidney disease: perhaps no more. Journal of the American Society of Nephrology, 19, 2047-51. Retrieved from:
<http://www.ncbi.nlm.nih.gov/pubmed/18923054>.

- Article suggesting that hypertension may cause progression renal dysfunction only in genetically susceptible individuals (MYH9 haplotype) or may be the result of a primary renal disease. While it is well-recognized that elevated blood pressure can exacerbate existing chronic kidney disease, essential hypertension as the etiology of kidney damage may not be supported by current data.

Freedman, BI et al. (1995). The link between hypertension and nephrosclerosis. American Journal of Kidney Disease, 25, 207-21. Retrieved from:
<http://www.ncbi.nlm.nih.gov/pubmed/7847347>.

- Review article of the correlation between hypertension and renal processes resulting in nephrosclerosis and end-stage renal disease. Suggests that patients with hypertensive nephrosclerosis have contributing mechanisms that increase their susceptibility to progressive renal disease, including primary renal microvascular diseases, renal artery stenosis, and/or genetic factors.

Luft, FC et al. (2000). Hypertensive nephrosclerosis: a cause of end-stage renal disease? Nephrology Dialysis Transplantation, 15, 1515-17. Retrieved from:
<http://www.ncbi.nlm.nih.gov/pubmed/11007815>.

- Editorial questioning the connection between essential hypertension and nephropathy. The author proposes that many factors contribute to

nephropathy, including obesity, hyperlipidemia, and genetics; still, blood pressure is a controllable and treatable factor that can prevent progression of renal disease.

Marcantoni, C et al. (2002). Hypertensive nephrosclerosis in African Americans versus Caucasians. *Kidney International*, 62, 172-80. Retrieved from:
<http://www.ncbi.nlm.nih.gov/pubmed/12081576>.

- Retrospective study comparing renal biopsies with a histological diagnosis of hypertensive nephrosclerosis among African American versus Caucasian patients. Though MAP and proteinuria were similar between groups, African American patients were found to have more severe histological findings. This again suggests other contributing factors such as genetics and microvascular disease.

1.6.3. Renovascular and other vascular diseases

Ruggenenti, et al (2011). Chapter 34: Microvascular and Macrovascular Diseases of the Kidney. Brenner & Rector's The Kidney Ninth Edition; p. 1297-331.

- Review of microvascular diseases: thrombotic microangiopathies (Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura), atheroembolic renal disease, radiation nephropathy, and renal involvement in systemic diseases (Scleroderma, Sickle Cell Disease, and the Antiphospholipid Syndrome)
- Review of macrovascular diseases: acute occlusion of the renal artery, aneurysms of the renal artery, and thrombosis of the renal vein

1.6.4. Tubular and interstitial diseases

Kelly, et al (2011). Chapter 35: Tubulointerstitial Diseases. Brenner & Rector's The Kidney Ninth Edition; p. 1332-55.

- Review of etiology and pathology of acute interstitial nephritis and chronic tubulointerstitial nephritis

1.7. Polycystic kidneys

Takier V, et al (2011) Polycystic Kidney Disease: Pathogenesis and Potential Therapies.

Biochim Biophys Acta. 1812 (10): 1337-1342. Retrieved from

<http://www.ncbi.nlm.nih.gov/pubmed/21146605>

- Review discussing the pathogenic pathways and therapeutic treatments of polycystic kidney disease.

Mosconi G, et al (2013) Renal Transplant in Patients with Polycystic Disease: The Italian Experience. Transplantation Proceedings; 45:2635-2640. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/24034011>.

- Analysis of outcomes in renal transplant recipients with polycystic kidney disease.

Patel P, et al (2011) Native nephrectomy in transplant patients with autosomal dominant polycystic kidney disease. Ann R Coll Surg Engl; 93:391-395. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/21943464>.

- Clinical outcomes at an institution practicing native nephrectomy in patients with autosomal polycystic kidney disease. The study concluded that native nephrectomy was not needed in the majority of patients.

Serra AL, et al (2010) Sirolimus and kidney growth in autosomal dominant polycystic kidney disease. N Engl J Med 363(9): 820-829. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/20581391>.

- A clinical trial using sirolimus in adults with autosomal dominant polycystic kidney disease. The study showed that 18 months of treatment with sirolimus did not halt polycystic kidney growth.

Jacquet A, et al (2011) Outcomes of renal transplantation in patients with autosomal dominant polycystic kidney disease: a nationwide longitudinal study. *Transplant International* 24:582-587. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/21352383>.

- Results from a nationwide study showing that patients with autosomal dominant polycystic kidney disease are associated with better graft survival, more thromboembolic complications, more metabolic complications and increases rates of hypertension.

1.8. Chronic calcineurin inhibitor toxicities

CNI and CAN

Ekberg, H et al. (2007). Reduced exposure to calcineurin inhibitors in renal transplantation (ELITE-Symphony Study). *New England Journal of Medicine*, 357, 2562-75. Retrieved from:
<http://www.ncbi.nlm.nih.gov/pubmed/18094377>.

- Kidney transplant recipients were randomly assigned to one of four treatment groups: standard-dose cyclosporine, low-dose cyclosporine, low-dose tacrolimus, or low-dose sirolimus group. All patients in low-dose groups received daclizumab induction, and maintenance immunosuppression consisted of mycophenolate mofetil and corticosteroids in all groups. Superior graft outcomes were seen with low-dose tacrolimus, with significantly higher eGFR, higher allograft survival, and lower rates of acute rejection episodes at 12 months post-transplant.

Flechner, SM et al. (2004). De novo kidney transplantation without use of calcineurin inhibitors preserves renal structure and function at two years. *American Journal of*

Transplantation, 4, 1176-85. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/15476476>.

- Kidney transplant recipients were randomized to a cyclosporine-based or sirolimus-based immunosuppressive regimen following basiliximab induction, in combination with mycophenolate mofetil and prednisone. Patients on sirolimus-based regimens had a lower incidence of chronic allograft nephropathy (CAN) and better renal function at 2 years, with similar patient outcomes, graft outcomes, and acute rejection rates.

Flechner, SM et al. (2008). Calcineurin inhibitor-sparing regimens in solid organ transplantation: focus on improving renal function and nephrotoxicity. Clinical Transplantation, 22, 1-15. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/18217899>.

- Review of acute and chronic nephrotoxicity and cardiovascular morbidity associated with calcineurin inhibitors and the impact of calcineurin-sparing strategies in kidney, liver, and heart transplantation. In kidney transplantation, several studies have demonstrated modest improvements in renal function but histological damage is observed for the duration that the calcineurin inhibitors are continued, despite dose minimization.

Nausens, M et al. (2009). Calcineurin inhibitor nephrotoxicity. Clinical Journal of the American Society of Nephrology, 4, 482-508. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/19218475>.

- Review article of the clinical and histologic features of acute and chronic calcineurin inhibitor nephrotoxicity as well as susceptibility factors for nephrotoxicity, including supratherapeutic levels of cyclosporine or

tacrolimus, older kidney age, use of NSAIDs, and certain genetic polymorphisms. The article also includes considerations for prevention and treatment of calcineurin inhibitor-induced nephrotoxicity.

Weir, MR et al. (2001). Long-term impact of discontinued or reduced calcineurin inhibitor in patients with chronic allograft nephropathy. *Kidney International*, 59, 1567-73.

Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/11260422>.

- In patients with declining kidney function due to biopsy-proven chronic allograft nephropathy, calcineurin inhibitor dose was reduced or completed discontinued with the addition, continuation and/or increased dose of mycophenolate mofetil and corticosteroids. Although intervention slowed the rate of graft deterioration and was associated with a minimal incidence of acute rejection, concomitant strategies such as intensive blood pressure and glucose control should be considered.

CNI and Metabolic Disorders

Artz, MA et al. (2003). Improved cardiovascular risk profile and renal function in renal transplant patients after randomized conversion from cyclosporine to tacrolimus. *Journal of the American Society of Nephrology*, 14, 1880-88. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/12819249>.

- Stable kidney transplant recipients (>1 year post-transplant, CrCl > 20 ml/min) were randomized to either continuation of cyclosporine or conversion to tacrolimus, with a follow-up of 6 months. Tacrolimus conversion was associated with a significant reduction in blood pressure, LDL cholesterol, and triglycerides. While the incidence of NODAT is higher with tacrolimus, glucose and HbA1c levels were similar between groups.

Drachenberg, CB et al. (1999). Islet cell damage associated with tacrolimus and cyclosporine: morphological features in pancreas allograft biopsies and clinical correlation. *Transplantation*, 15, 396-402. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/10459544>.

- Describes the beta cell structural damage caused by tacrolimus and cyclosporine, particularly at higher levels and with concomitant steroid therapy.

Kasiske, BL et al. (2003). Diabetes mellitus after kidney transplantation in the United States. *American Journal of Transplantation*, 3, 178-85. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/12603213>.

- Report of data from the United Renal Data System describing the incidence, risk factors, and clinical relevance of new-onset diabetes after transplantation (NODAT). Risk factors for NODAT included age, African American and Hispanic race, male donor, increasing HLA mismatches, BMI > 30 kg/m², and the use of a tacrolimus-based initial maintenance immunosuppressive regimen. Factors that reduce the risk of NODAT included, among others, the use of an antimetabolite.

Margreiter, R et al. (2002). Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: a randomised multicenter study. *Lancet*, 359, 741-46. Retrieved from: <http://www.ncbi.nlm.nih.gov/pubmed/11888584>.

- Kidney transplant recipients were randomized to de novo tacrolimus or cyclosporine in combination with azathioprine and corticosteroids. Regarding the cardiovascular-risk profile, tacrolimus-based regimens were

associated with a lower incidence of hypertension and hypercholesterolemia.

Murakami N, Riella LV, Funakoshi T. Risk of metabolic complications in kidney transplantation after conversion to mTOR inhibitor: a systematic review and meta-analysis. Am J Transplant. 2014;14(10):2317-27. Retrieved from:
<https://www.ncbi.nlm.nih.gov/pubmed/25146383>

- Systematic review of nine trials converting patients from CNI to mTOR (n= 2323) with the primary end points of new-onset diabetes after transplant (NODAT) and hypercholesterolemia. Relative risk of NODAT and hypercholesterolemia associated with mTOR inhibitors was lower than with CNI-based regimen, but there was a higher risk of acute rejection, proteinuria and anemia associated with mTOR inhibitor conversion.

Vincenti, F et al. (2007). Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. American Journal of Transplantation, 7, 1506-14. Retrieved from:

<http://www.ncbi.nlm.nih.gov/pubmed/17359512>.

- Nondiabetic kidney transplant recipients were randomized to cyclosporine microemulsion or tacrolimus in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids. NODAT or impaired fasting glucose at 6 months post-transplant was significantly lower though LDL and triglyceride levels were significantly higher with cyclosporine microemulsion compared to tacrolimus; overall, both groups had similar graft outcomes, patient outcomes, and rejection rates.