1. Kidney transplantation

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1.1 Induction therapy

Masset, C., et al. (2020) Induction therapy in elderly kidney transplant recipients with low immunological risk. Transplantation 2020; 104(3), 613-622. Retrieved from: https://journals.lww.com/transplantjournal/Fulltext/2020/03000/Induction_Therapy_in_Elderly_Kidney_Transplant.31.aspx

- This multicenter study compared survival and clinical outcomes in elderly (≥ 65 YO) kidney transplant recipients at low immunological risk who received rATG (1.5 mg/kg/day- maximum 75 to 100 mg/d) vs. basiliximab (20 mg IV POD 0 and 4) induction therapy
- Patient and graft survival at 3 years were not significantly different between the 2 groups (74 vs. 68%)
- There was a significantly higher incidence of post-transplant diabetes in the basiliximab group associated with higher FK trough levels at 3 months

Alloway RR et al. (2019) Rabbit anti-thymocyte globulin for the prevention of acute rejection in kidney transplantation. Am J Transplant. 2019: 19(8); 2252-2561. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6767488/

- Results of 2 international randomized trials consisting of 508 total kidney transplant recipients looking at ATG vs. basiliximab with composite end point of BPAR, death, graft loss or loss to follow up
- Pooled analysis supports non-inferiority between these agents for induction therapy
- Further meta analysis of 7 trials suggests ATG may have a lower BPAR rate at 12 months

Singh N et al. (2018) Tailored Rabbit Antithymocyte Globulin Induction Dosing for Kidney Transplantation. Transplant Direct. 2018: 4(2):e343. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed?term=29464204

- Evaluated cumulative conventional dosing for induction using rabbit ATG (6-10 mg/kg) vs. reduced dosing (4.5 mg/kg) in a five year retrospective cohort consisting of 224 kidney transplant recipients
- Cumulative dosing of 3mg/kg was given to non-sensitized living donor recipients, 4.5 mg/kg was given to non-sensitized deceased donor recipients and 6 mg/kg was given to high immunological risk patients
- No differences in patient or graft survival or infection risk between the 3 groups

Hill P, Cross N, Barnett N, et al. (2017) Polyclonal and monoclonal antibodies for induction therapy in kidney transplant recipients. Cochrane systemic review. 2017. Retrieved from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004759.pub2/abstract

- A cochrane review and analysis of monoclonal and polyclonal antibodies used for kidney transplant induction, excluding IL2RAs
- Alemtuzumab and ATG both prevent rejection, and rejection rates without induction therapy were 45%
- Induction therapy is associated with an increased risk of infection without any impact on patient mortality

Koyawala N, Silber JH, Rosenbaum PR, et al. (2017) Comparing Outcomes between Antibody Induction Therapies in Kidney Transplantation. J Am Soc Nephrol 2017; 28:2188. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed?term=28320767

- Using OPTN and medicare claims data compared outcomes for rabbit ATG, basiliximab and alemtuzumab in 1:1 pairs. Primary outcome was death and death or allograft failure.
- Compared to rATG, alemtuzumab had a higher rate of death and death or allograft failure, which was consistent even among subgroups
- Compared to rATG, basiliximab had a higher rate of death and death or lymphoma
- rATG may be associated with a lower risk of side effects and mortality

Thomusch O et al. (2016) Rabbit-ATG or basiliximab induction for rapid steroid withdrawal after renal transplantation (Harmony): an open-label, multicentre, randomised controlled trial. Lancet. 2016; 388(10063): 3006-3016. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed?term=27871759

- Open label multi center trial randomizing low immunological risk kidney transplant patients to receive basiliximab induction with low dose tacrolimus, mycophenolate mofetil and maintenance corticosteroids, rapid corticosteroid withdrawal on day 8, or rapid corticosteroid withdrawal on day 8 after rabbit ATG induction.
- BPAR rates at 1 year did not differ between use of basiliximab or rabbit ATG induction therapy with rapid steroid withdrawal

Haynes R, Harden P, Judge P, et al. (2014) 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.

Ejaz NS, Shields AR, Alloway RR, et al. (2013) 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.

Gabardi, S et al. (2011) 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.

Farney AC, Doares W, Rogers J, et al. (2009) 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.

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.

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.

1.2 Maintenance therapy

Woodle ES, et al. (2020) BEST Study Group. Belatacept-Based Immunosuppression With Simultaneous Calcineurin Inhibitor Avoidance and Early Corticosteroid Withdrawal: A Prospective, Randomized Multicenter Trial. American Journal of Transplantation. 2020; 00:1–17. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7004468/

- This prospective, randomized, open-label trial compared two belatacept-based calcineurin inhibitor avoidance/early corticosteroid withdrawal regimens with tacrolimus-based early corticosteroid withdrawal regimens.
- Patients were randomized to receive alemtuzumab/belatacept, rATG/belatacept, or rATG/tacrolimus. Superiority was not found for the primary composite endpoint of patient death, renal graft loss, or MDRD eGFR < 45 at 12 months.
- No significant differences were found for antibody-mediated rejection, biopsy-proven mixed acute rejection, de-novo DSA production, death, death-censored graft loss, eGFR < 45. There were statistically significant higher rates of acute cellular rejection in the belatacept groups versus the tacrolimus group. Additionally, there was a lower incidence of neurologic and electrolyte abnormalities with belatacept.

Manzia TM, Carmellini M, et al. (2020) A 3-month, Multicenter, Randomized, Open-label Study to Evaluate the Impact on Wound Healing of the Early (vs Delayed) Introduction of Everolimus in De Novo Kidney Transplant Recipients, With a Follow-up Evaluation at 12 Months After Transplant (NEVERWOUND Study). Transplantation. 2020; 104(2), 374. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7004468/

- This multicenter, randomized, open-label study of 394 kidney transplant recipients evaluated whether a delayed EVR-based regimen reduced the risk of wound-healing complications versus EVR started immediately post-kidney transplant.
- Patients were randomized to either EVL with low-dose cyclosporine and steroids immediately post-transplant or were converted from cyclosporine, MMF, and steroids at 28 $\pm$ 4 days.
- At 3 months, WHC-free rates in the immediate EVR vs. delayed EVR arm were 0.68 (95% confidence interval [CI], 0.62-0.75) versus 0.62 (95% CI, 0.55-0.68) (log-rank *P* = 0.56). There were no significant differences between the 3- and 12-month treatment failure rates, delayed graft function and renal function, and patient and graft survival rates.

Berger S, Sommerer C, Witzke O, et al. (2019) Two-year outcomes in de novo renal transplant recipients receiving everolimus-facilitated calcineurin inhibitor reduction regimen from the TRANSFORM study. Am J Transplant. 2019; 19(11): 3018 3034.
Retrived from: https://onlinelibrary.wiley.com/doi/full/10.1111/ajt.15480

- Two year results of a prospective open label trial looking at reduced exposure of CNI + everolimus vs. standard CNI and mycophenolate and impact on a composite of BPAR and eGFR <50
- Everolimus + reduced CNI was non-inferior in primary end point, and was associated with less DSAs, CMV infections and BK virus infections

Fructuoso, AS et al. (2019). Effectiveness and safety of the conversion to MeltDose® extended-release tacrolimus from other formulations of tacrolimus in stable kidney transplant patients: a retrospective study. Clinical Transplantation. e13767. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31815310

- Analysis of the efficacy and safety of conversion from immediate-release tacrolimus or prolonged-release tacrolimus to once-daily MeltDose® extended-release tacrolimus in kidney transplant recipients. The total daily dose was reduced by 35% after 3 months with a cost reduction of 63% observed. There were no changes in renal function, no cases of biopsy proven acute rejection, and reports of tremors decreased after the conversion to the MeltDose®.

Bray RA et al. (2018) De novo donor-specific antibodies in belatacept-treated vs cyclosporine-treated kidney-transplant recipients: Post hoc analyses of the randomized phase III BENEFIT and BENEFIT-EXT studies. Am J Transplant. 2018; 18(7): 1783-1789. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29509295

- Post Hoc analysis of the BENEFIT and BENEFIT-EXT trials where kidney transplant recipients had the presence or absence of HLA-specific antibodies determined at baseline and at certain time points up to the end of 84 month follow up including times of clinically suspected acute rejection episodes. In this analysis, samples were further tested to determine presence/absence of DSAs and mean fluorescence intensity (MFI)
- In the BENEFIT and BENEFIT EXT trials DSAs developed in a significantly higher amount of cyclosporine treated patients vs. belatacept groups over 7 years in both studies. In patients developing de novo DSAs, belatacept group had a numerically lower MFI vs. cyclosporine group.

Tremblay S et al. (2017) A steady-state head-to-head pharmacokinetic comparison of all FK-506 (tacrolimus) formulations (ASTCOFF): an open label, prospective, randomized, two-arm, three-period crossover study. Am J Transplant. 2017;17(2):432-442. retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27340950

- An open label single center trial evaluating pharmacokinetics of all three available tacrolimus formulations (IR-Tac, ER-Tac and LCPT). AUC and overall bioavailability were

significantly higher for LCPT vs. IR-Tac and ER-Tac formulations. Intraday fluctuations in peak to trough were lower for LCPT vs. IR-Tac and ER-Tac formulations and there were lower concentration peaks. IR-Tac and ER-Tac formulations displayed similar pharmacokinetic profiles. No deaths, episodes of biopsy proven rejection, graft loss or serious adverse events were observed.

- Conversion factors of 1:1:0.80 for IR-Tac:ER-Tac:LCPT were utilized in this study

Trofe-Clark J et al. (2017) Results of ASERTAA, a Randomized Prospective Crossover Pharmacogenetic Study of Immediate-Release Versus Extended-Release Tacrolimus in African American Kidney Transplant Recipients. Am J Kidney Dis. 2017: 71(3); 315-326. Retrieved from: https://www.ajkd.org/article/S0272-6386(17)30897-1/fulltext

- Evaluated the relationship between CYP3A5 genotype and AUC of tacrolimus IR vs. LCPT in 50 African American kidney transplant patients in a pharmacokinetic study
- 80% of population were CYP3A5 expressers, no differences in AUC or Cmin when LCPT or IR-Tac was administered, however the Cmax of IR-Tac was 33% higher in expressers vs. non-expressers. This effect was not observed with LCPT, indicating that the delayed absorption profile of LCPT may attenuate risk of peak related side effect.

Budde K et al. (2017) Everolimus with cyclosporine withdrawal or low exposure cyclosporine in kidney transplantation from month 3: a multicenter randomized trial: HERAKLES study group. Nephrol Dial Transplant. 2017:32(6):1060-1070. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28605781

- Prospective, randomized, multicenter trial with 499 kidney transplant patients who were randomized at month 3 to remain on standard CNI with cyclosporine (+ MPA), convert to everolimus with MPA or start everolimus with reduced CNI and no MPA.
- eGFR using the Nankivell equation at 12 month was significantly greater in CNI-free arm vs. standard CNI therapy and low CNI group with a mean difference of 5.6 mL/min/1.73 m2 and 5.5 mL/min/1.73 m2 respectively. There were no differences in BPAR between groups.

Adams AB et al. (2017) Belatacept combined with transient calcineurin inhibitor therapy prevents rejection and promotes improved long-term renal allograft function. Am J Transplant. 2017; 17(11): 2922-2936. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/

- A retrospective analysis of 745 patients undergoing renal transplant and receiving Belatacept compare d to a historical cohort receiving a tacrolimus-based immunosuppression regimen. Patient and graft survival were similar between groups. Belatacept treatment was associated with superior renal function and there were no differences in serious infections. In the early Belatacept groups treated with the regimen from the BENEFIT trial, an increased rate of acute rejection was observed. With the addition of a transient course of tacrolimus, rejection rates reduced and were similar to the historical cohort.

Huh KH et al. (2017). De novo low-dose sirolimus versus mycophenolate mofetil in combination with extended-release tacrolimus in kidney transplant recipients: a multicenter, open-label, randomized, controlled, non-inferiority trial. Nephrol Dial Transplant; 32(8):1415-1424. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28810721

- 158 renal transplants randomized to receive low-dose sirolimus or MMF in combination with ER tacrolimus. Low dose sirolimus with ER tacrolimus was not inferior to MMF and ER tacrolimus with respect to safety and efficacy.

Vincenti F. (2017) Ten-year outcomes in a randomized phase II study of kidney transplant recipients administered belatacept 4-weekly or 8-weekly. Am J Transplant. 2017; 17(12): 3219-3227. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28758341

- Estimated GFR values 10 years from randomization for 4-weekly belatacept, 8-weekly belatacept, and cyclosporine were 67, 68.7, and 42.7 mL/min per 1.73m2 respectively. The rate of biopsy proven acute rejection was 2 times higher in patients receiving belatacept every 8 weeks compared to every 4 weeks.

Haller MC, Royuela A, Nagler EV, Pascual J, Webster AC. (2016) 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.

Thierry A, Lemeur Y, Ecotière L, et al. (2016) 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.

Durrbach A, Pestana JM, Florman S, et al. (2016) 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.

Rostaing L, Bunnapradist S, Grinyó JM, et al. (2016) 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.

Vincenti F. (2016) 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, et al. (2015) 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.

Xie X, et al. (2015) 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.

Budde K, Lehner F, Sommerer C, et al. (2015) 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. (2014) 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. (2014) 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.

Lim WH, Eris J, Kanellis J, et al. (2014) 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 1year 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.

Masson P, Henderson L, Chapman JR, Craig JC, Webster AC. (2014) 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.

Silva HT, Felipe CR, Garcia VD, et al. (2013) 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.

Ho, ET 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.

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.

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.

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).

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.

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).

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.

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.

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.

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.

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.

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.

1.3 Desensitization therapy

Tremblay S, Driscoll JJ, et al. (2020) A prospective, iterative, adaptive trial of carfilzomib-based desensitization. American Journal of Transplantation. 2020; 20(2), 411-421. Retrieved from: https://onlinelibrary.wiley.com/doi/full/10.1111/ajt.15613

- This prospective, non-randomized study evaluated the efficacy of carfilzomib for desensitization in 16 highly sensitized kidney transplant candidates. KTR in group A received 12 increasing doses of carfilzomib from 20 mg/m2 to 36 mg/m2, preceded by 50 – 100 mg methylprednisolone. Following the last carfilzomib dose, patients underwent 3 sessions of plasmapheresis. KT candidates in group B received the same regimen with additional plasmapheresis once weekly prior to carfilzomib.
- The safety profile of carfilzomib was found to be similar to bortezomib, but neurotoxicity was not present with carfilzomib. There was a significant reduction in HLA immunodominant antibodies in group A. Rebound occurred, with antibody levels returning to baseline values at days 81 and 141. 69.2% of bone-marrow plasma cells were depleted following carfilzomib monotherapy.

Lonze BE et al. (2018). IdeS (Imlifidase): A novel agents that cleaves human IgG and permits successful kidney transplantation across high-strength donor-specific antibody. Ann Surg; 268(3):488-496. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/20004918

- Single-center experience with 7 highly sensitized kidney transplant candidates with positive crossmatches who received IdeS prior to transplant.
- All crossmatches became negative. 3 patients had DSA rebound and AMR, which was treated. 3 had delayed graft function that resolves. At the 235 day follow-up mark, all had functioning allografts.

Jordan SC et al. (2017). IgG Endopeptidase in highly sensitized patients undergoing transplantation. N Engl J Med; 377(5):442-453. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28767349

- IdeS was administered to 25 highly sensitized patients before receiving a kidney from a HLA-incompatible donor. IdeS was found to reduce/eliminate donor specific antibodies in 24 of 25 patients. Antibody mediated rejection occurred in 10 patients, but all responded to treatment. There was one graft loss due to non-HLA antibodies.

Jeong JC, Jambaldorj E, Kwon HY, et al. (2016) 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.

Vo AA, Choi J, Cisneros K, et al. (2014) 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. (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

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)

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

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)

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

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)

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

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

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%

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

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 ± 19% before to 44 ± 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

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

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

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.

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

1.4 Management of rejection

Bailly E, et al. (2020) An extension of the RITUX-ERAH study, multicenter randomized clinical trial comparing rituximab to placebo in acute antibody-mediated rejection after renal transplantation. Transplant International 2020. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/32279367

- 7 year outcomes of the RITUX-ERAH study (11 patients received placebo and 27 patients with ≥ 1 dose of rituximab)
- Death-censored kidney allograft survival and renal function not significantly different between the groups
- Similar development of anti-HLA sensitization in both groups
- NS difference in neoplastic complications but 7 cancers in 6 patients s/p rituximab

Pottebaum A, et al. (2020) Efficacy and Safety of Tocilizumab in the Treatment of Acute Active Antibody Mediated Rejection in Kidney Transplant Recipients. Transplantation Direct 2020; 6(4). Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/32309629

- Single-center, observational study of kidney transplant recipients s/p ≥ 1 dose tocilizumab for acute AMR
- 7 patients received tocilizumab 8 mg/kg (max dose 800 mg) monthly, leading to ≥ 50% reduction in immunodominant DSAs in 4/6 patients
- Stabilization of renal function during therapy
- Extended follow-up: 1 patient with mixed rejection and 2 patients with ACR 6-24 mos s/p tocilizumab

Marks WH, et al. (2019) Safety and efficacy of eculizumab in the prevention of antibody-mediated rejection in living-donor kidney transplant recipients requiring desensitization therapy: A randomized trial. American Journal of Transplantation 2019; 19(10), 2876-2888. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6790671/

- Phase 2, randomized, multicenter, open-label, double-arm study
- Evaluated the safety and efficacy of eculizumab in for prevention of AMR in sensitized recipients of living donor kidney transplants
- Post-transplant 51 patients received standard of care (PLEX/IVIg) and 51 patients received eculizumab
- Eculizumab dosing: 1200 mg immediately before reperfusion; 900 mg on post-transplant days 1, 7, 14, 21, and 28; and 1200 mg at weeks 5, 7, and 9
- Significantly decreased treatment failure inclusive of grade I AMR in eculizumab (11.8%) vs. standard of care (29.4%) groups

Tan EK, et al. (2019) Use of Eculizumab for Active Antibody-mediated Rejection That Occurs Early Post kidney Transplantation: A Consecutive Series of 15 Cases. Transplantation 2019; 103(11), 2397-2404. Retrieved from: https://journals.lww.com/transplantjournal/Fulltext/2019/11000/Use_of_Eculizumab_for_Active_Antibody_mediated.34.aspx

- This observational retrospective study of kidney transplant recipients investigated the role of eculizumab for AMR treatment within the first 30 days post-transplant
- 15 patients with AMR (13/15 biopsy-proven AMR) treated with eculizumab + plasmapheresis
- Within 1 week of eculizumab treatment, eGFR significantly increased and persistent AMR in 16.7% at 4-6 months

Glotz D, et al. (2019) Safety and efficacy of eculizumab for the prevention of antibody-mediated rejection after deceased-donor kidney transplantation in patients with preformed donor-specific antibodies. American Journal of Transplantation 2019; 19(10), 2865-2875. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/31012541

- Open-label, single-arm trial to determine safety and efficacy of eculizumab in prevention AMR in deceased-donor kidney transplants with preformed DSA
- Eculizumab dosing: 1200 mg immediately before reperfusion; 900 mg on post-transplant days 1, 7, 14, 21, and 28; and 1200 mg at weeks 5, 7, and 9
- Treatment failure rate (composite of biopsy-proved grade II/III AMR (Banff 2007 criteria), graft loss, death, or loss to follow-up) by 9 weeks post-transplant significantly lower with eculizumab (8.8%) versus standard of care (40%)
- Patient and graft survival rates 91.5% and 83.4% in cohort

Schinstock CA, et al. (2019) Long-term outcomes of eculizumab-treated positive crossmatch recipients: Allograft survival, histologic findings, and natural history of the donor-specific antibodies. American Journal of Transplantation 2019; 19(6), 1671-1683.
Retrieved from: https://onlinelibrary.wiley.com/doi/full/10.1111/ajt.15175

- This observational, retrospective study determined long-term outcomes of eculizumab-treated positive crossmatch kidney transplant recipients vs. positive cross-match and negative cross-match controls

- Death-censored allograft survival rates similar in both positive cross-match groups but significantly reduced vs. negative cross-match controls
- Eculizumab-treated group:
    - 57.9% allografts developed chronic AMR
    - Death-censored allograft survival 76.6% at 5 years and 75.4% at 7 years
    - IgG3, BFXM $\geq$ 300, and C1q positivity associated with allograft loss

Schinstock CA, et al. (2019) Recommended Treatment for Antibody-mediated Rejection After Kidney Transplantation: The 2019 Expert Consensus From the Transplantion Society Working Group. Transplantation, 104(5), 911-922. Retrieved from: https://journals.lww.com/transplantjournal/Fulltext/2020/05000/Recommended_Treatment_for_Antibody_mediated.11.aspx?context=LatestArticles

- The pre-publication TTS guidelines for management of AMR in kidney transplant recipients describes consensus recommendations for appropriate treatment of active and chronic AMR. Treatment recommendations are based on expert opinion, as well as evidence that is currently available in kidney transplant

Choi J et al. (2017). Assessment of Tocilizumab (Anti–Interleukin-6 Receptor Monoclonal) as a Potential Treatment for Chronic Antibody-Mediated Rejection and Transplant Glomerulopathy in HLA-Sensitized Renal Allograft Recipients. American Journal of Transplantation, 17(9): 2381-2389. Retrieved from: https://onlinelibrary.wiley.com/doi/full/10.1111/ajt.14228

- Tocilizumab patients demonstrated graft survival and patient survival rates of 80% and 91% at 6 years. Significant reductions in DSAs and stabilization of renal function were seen at 2 years.

Moresco F et al. (2017). Treatment of chronic antibody mediated rejection with intravenous immunoglobulins and rituximab: A multicenter, prospective, randomized, double-blind clinical trial. American Journal of Transplantation, 18(4): 927-935. Retrieved from: https://onlinelibrary.wiley.com/doi/full/10.1111/ajt.14520

- Multicenter, prospective, randomized, placebo-controlled, double-blind trial to evaluate efficacy and safety of intravenous immunoglobulins (IVIG) combined with rituximab (RTX)
- The combination of IVIG and RTX is not useful in patients displaying transplant glomerulopathy and DSA

Sautenet B, Blancho G, Büchler M, et al. (2016) 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.

Montgomery RA et al. (2016) Plasma-Derived C1 Esterase Inhibitor for Acute Antibody-Mediated Rejection Following Kidney Transplantation: Results of a Randomized Double-Blind Placebo-Controlled Pilot Study. Am J Transplant. 2016:16(12);3468-3478. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/27184779

- Phase 2B randomized placebo-controlled pilot study evaluating human plasma derived C1-esterase inhibitor (C1 INH) vs. placebo in 18 patients.
- The primary end point of a difference between groups in day 20 pathology or graft survival was not achieved, however the C1 INH group had a trend toward sustained improvement in renal function. There were no graft losses, deaths or serious study drug related ADE.

Kim M, Martin ST, Townsend KR, Gabardi S. (2014) 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

Cooper JE, et al. (2014) 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.

Eskandary F, Bond G, Schwaiger E, et al. (2014) 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 × 1.3 mg/m2 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)

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)

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.

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

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)

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

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

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

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.

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

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

Raghavan R, Jeroudi A, Achkar K, Gaber AO, Patel SJ, Abdellatif A. (2010) 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

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

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

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.

- Evidence-based recommendations for the treatment of 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)

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

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 ± IVIG ± rATG ± methylprednisolone ± 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

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)

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)

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

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

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

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.

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

Lehrich RW, Rocha PN, Reinsmoen N, et al. (2005) 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.

Shah A, Nadasdy T, Arend L, et al. (2004) 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 an rATG is an effective means of reversing AHR in renal allograft

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

Montgomery RA, Zachary AA, Racusen LC, et al. (2000) 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.

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)

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

Alarcon-zurita A, Ladefoged J. (1976) 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 suggests that total methylprednisolone dosage exceeding 3 to 5 g did not lead to significant improvement and therefore does not warrant the additional risk.

1.5 Retransplantation and Graft Failure

Benko T et al. (2019). Long-term outcome of third, fourth, and fifth kidney transplantation: technical aspects and immunological challenges. Clin Kidney J; 12(6):895-900. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/31807305

- Kidney recipients that underwent a third, fourth, or fifth kidney transplant were compared to a historical cohort of recipients transplanted a second time. No differences in graft and patient survival were observed, suggesting that survival after more than three transplants in similar to that of second graft recipients.

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.

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.

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.

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.

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.

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

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.

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.

1.6.2 Focal Segmental Glomerulosclerosis

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.

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.

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.

1.6.3 Lupus Nephritis

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.

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).

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.

1.6.4 Membranous Glomerulonephritis

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.

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.

1.6.5 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.

1.6.6 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.

1.6.7 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.

1.6.8 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.

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.

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.

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).

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.

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.

1.6.9 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

1.6.10 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

1.6.11 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.

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.

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.

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.

1.7 Chronic calcineurin inhibitor toxicities

1.7.1 CNI and CAN

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.

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.

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.

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.

1.7.2 CNI and Metabolic Disorders

Wissing KM et al. (2018). Prospective randomized study of conversion from tacrolimus to cyclosporine A to improve glucose metabolism in patients with posttransplant diabetes mellitus after renal transplantation. Am J Transplant, 18(7):1726-1734. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29337426

- Multicenter, prospective study to assess whether conversion from tacrolimus to cyclosporine can reverse posttransplant diabetes (PTDM) after renal transplantation. At 12 months, 39% of patients on cyclosporine were off glucose lowering medications compared to 13% of patients in the tacrolimus group. The replacement of tacrolimus with cyclosporine significantly improved glucose metabolisms and may reverse PTDM in the first year after converting to cyclosporine.

Holdaas H et al. (2017). Cardiovascular parameters to 2 years after kidney transplantation following early switch to everolimus without calcineurin inhibitor therapy: an analysis of the randomized ELEVATE study. Transplantation; 101(10):2612-2620. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/28333860.

- Patients were randomized at 10-14 weeks post-transplant to convert from CNI to everolimus or continue on standards CNI therapy. No clinically relevant effects on cardiac endpoints were seen after converting to a CNI-free regimen.

Murakami N, Riella LV, Funakoshi T. (2014) 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 trail 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.

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.

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.

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.

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.