1. Kidney transplantation

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1.1 Induction therapy


- Retrospective, single center trial comparing induction treatments in low-immune risk kidney transplant recipients
- There was no difference found between patients treated with IL2 receptor antagonists and no induction therapy. Suggests no form of induction therapy is necessary for zero HLA mismatch transplant recipients with relatively no other immunologic risks
- Use of induction therapy with T cell–depleting therapy or IL-2 receptor antagonists in first kidney transplant recipients who are well matched with their donor at the HLA-A, -B, -DR, -DQB1 gene loci is not associated with improved post-transplant outcomes


- A single-center, randomized study comparing safety and efficacy of low-dose thymoglobulin (3 mg/kg total) to basiliximab (20 mg on D0 and D4) induction with tacrolimus (target trough first 6 months 8-10 ng/mL), MMF 2g/day, steroid taper for maintenance immunosuppression
- No difference between groups (thymoglobulin vs. basiliximab) in patient survival (100% vs. 98.1%) and graft survival (93.6% vs. 92.5%)
- No difference between groups (thymoglobulin vs. basiliximab) in biopsy proven acute rejection (6.4% vs. 3.8%), delayed graft function (4.3% vs. 3.8%), slow graft function (3.4% vs. 5.7%) and 12-month leukopenia (21.3% vs. 11.3%)

  - A meta-analysis of 11 studies, n=2886, split into two groups; group A included studies that used the same dose of tacrolimus in both arms and group B included studies that used induction and low-dose tacrolimus vs. no induction and high-dose tacrolimus
  - IL2-RA induction is not associated with better outcomes in patients on tacrolimus-based immunotherapy (with or without corticosteroids); no difference in acute rejection rates or graft survival within both groups as well as within each group

  - Assessment of outcomes from the British Renal Transplant Registry
  - Compared patients who received IL-2RA induction vs no induction. There was no difference in eGFR at 1 year post-transplant, graft survival at 1 year and 5 years post-transplant, and patient survival at 1 year and 5 years post-transplant
  - Subgroup analysis comparing IL-2RA induction vs no induction in steroid-free vs triple immunosuppression also found no difference in outcomes

  - Grouped based off rituximab dose, either 200 mg or 375 mg/m²
  - Outcomes of 5 trials (n=390) did not differ in GFR rates, graft loss, AMR, T-cell mediated rejection, fungal infections, and patient survival rates. Incidence of infection was significantly less in the 200 mg group.

  - Scientific Registry of Transplant Recipients and Medicare claims from 1999-2016 for patients who received ATG or IL2RA for induction
  - HCV+ recipients were less likely to receive rATG, but those who did receive rATG had lower risk of acute rejection. There was no difference between induction therapies and risk of graft failure, death, liver transplant registration (prior history of liver transplant or on liver transplant waitlist), and cirrhosis

  - 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


Results of 2 international randomized trials consisting of 508 total kidney transplant recipients looking at rATG vs. basiliximab with composite end point of BPAR (biopsy-proven acute rejection), 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 rATG may have a lower BPAR rate at 12 months


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


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


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

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.


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.


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


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.


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.


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

• 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


• A retrospective, multicenter study evaluating weight-based dosing requirements of tacrolimus XR in de novo obese patients
• Of the 254 kidney transplant recipients, 81 (31%) were obese. The median therapeutic dose on POD7 was 0.1 vs. 0.12 vs. 0.14 mg/kg/day in the BMI > 30 kg/m2, BMI 25–30 kg/m2, and BMI < 25 kg/m2, respectively, (p = .0001). There was found to be strong linear relationship between ideal body weight (IBW) and therapeutic dose (r = .929)
• In both the non-obese and obese population, IBW was more strongly correlated to a therapeutic dose for tacrolimus XR


• A multicenter, prospective, observational study to compare the bioavailability of once-daily tacrolimus formulations in de novo kidney transplant recipients
• LCPT group (n=129) had a higher relative bioavailability, with similar Cmin, and 30% lower total daily dose compared against prolonged release-Tac (n=89) (P<0.001)
• Reported adverse events and renal function were similar between agents in the 6 month study


• 5-year follow-up post hoc analysis of a prospective trial including 288 patients comparing low dose tacrolimus combined with everolimus compared to standard of care with tacrolimus, mycophenolate, and prednisone
• The use of everolimus is associated with similar efficacy compared to mycophenolate in low-to-moderate immunologic risk kidney transplant recipients receiving tacrolimus
• The use of everolimus combined with reduced tacrolimus concentrations was associated similar rates of acute rejection, dnDSA, graft loss, and death, and stable renal function up to 5 years compared with the standard of care immunosuppressive regimen


• Randomized, multicenter trial with all recipients using rapid steroid withdrawal and grouped 1:1:1 to receive either belatacept with alemtuzumab, belatacept with rATG, or tacrolimus with rATG to assess the 2-year composite outcome of death, kidney allograft loss, or an eGFR <45 m/min/1.73m²
The composite outcome had no significant difference between groups, reflective of order above, 10%, 13%, and 21%.

Lower incidence of eGFR <45 occurred in both belatacept groups compared to tacrolimus (8%, 8%, and 19%), but significantly higher incidence of BPAR (19%, 25%, 7%)


Analysis of the Scientific Registry of Transplant Recipients for HIV+ recipients to compare those with early steroid withdrawal (ESW) to steroid continuation

ESW was utilized less in high-volume centers vs moderate-volume centers. The patient population was similar between both types of centers with regard to demographics and immunologic characteristics

Moderate-volume centers had higher rates of zero HLA mismatch and DGF

Acute rejection was more common with ESW, but there was no difference in death or graft failure


Multicenter, randomized control trial with 151 de novo recipients who received cyclosporine, mycophenolic acid, and steroids for 3-months and then were either grouped into early steroid withdrawal or cyclosporine replacement with everolimus with continued steroid use

No difference in 5-year patient and graft survival, cardiovascular outcomes, and malignancy. There was no difference in GFR at 1- or 5-years posttransplant in the intention-to-treat analysis; however, on-treatment analysis showed superior clearance in the everolimus cohort

Everolimus group had significantly more incidence of and more severe rejection and higher incidences of posttransplant diabetes


18-year follow-up of a randomized trial of 150 kidney transplant recipients, comparing 1:1:1 tacrolimus/sirolimus vs. tacrolimus/mycophenolate motif vs. cyclosporine/sirolimus. All patients received daclizumab induction

BPAR occurred less often in tacrolimus/mycophenolate group at 26% (vs. 36% in tacrolimus/sirolimus and 34% in the cyclosporine/sirolimus groups) with higher eGFR


5-year follow up study of low-risk, live-donor kidney transplant recipients who received alemtuzumab induction with maintenance belatacept and sirolimus therapy. Patients without evidence of rejection or donor-specific antibodies were eligible to wean to belatacept monotherapy at 12 months.

There was stable allograft function (mean eGFR 71 ± 19 mL/min/1.73 m²) and no allograft loss due to rejection at 5 years. 12/40 patients were weaned to belatacept monotherapy with controlled CMV and EBV reactivations, but 9/12 experienced transient BK in the first year with no clinical rejection

- 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.


- 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 ± 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.


- 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


- 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®.

- 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.

- 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

- 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.

- 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

• A retrospective analysis of 745 patients undergoing renal transplant and
receiving Belatacept compared 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,

• 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. 17(12): 3219-3227. Retrieved

• 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

• 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.

after renal transplantation comparing cyclosporine A/azathioprine or cyclosporine A/mycophenolate
mofetil bitherapy to cyclosporine A monotherapy: a 10-year postrandomization follow-up

• 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.


- 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.


- 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.


- 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.


- 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.


- 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.

- 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


- 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.


- 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.


- Systematic review of 29 randomized controlled trials comparing delayed conversion of mTOR for CNIs versus CNI continuation in kidney transplantation. Patients converted to mTOR up to 1 year post-transplant had higher GFR compared with those remaining on CNI, p < 0.001. However, the risk of rejection at 1 year and discontinuation secondary to adverse events was higher for mTORs.


- 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.


- 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.


- 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.


- 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.


- 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.


- 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).

- 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.


- 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.


- 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).


- 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.


- 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.

• 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.


• 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.


• 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.


• 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.


• 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


• A single-center, phase 2, open-label, single-arm exploratory study exploring the safety and limited efficacy of clazakizumab, a humanized anti-IL-6 monoclonal antibody, on highly sensitized patients awaiting kidney transplant
• Highly sensitized patients (n=20) received PLEX, IVlg, and clazakizumab 25 mg monthly for 6 months
• Clazakizumab was well tolerated and associated with reductions in class I and II donor specific antibodies (DSA) in 18 out of 20 patients with low incidence of DSA rebound. Three patients experienced an antibody-mediated rejection

- A retrospective, single-center trial comparing Obinutuzumab vs standard of care (Rituximab) on the effect of B-cell depletion and impact on crossmatch results in highly sensitized kidney transplant candidates
- Obinutuzumab effectively depleted B-lymphocytes in highly sensitized kidney transplant candidates and had no effect on the CDC crossmatch test results as opposed to rituximab


- Open-label, single-arm, phase 2 trial at 5 transplant centers to evaluate if 24-hour negative crossmatch occurred with median cPRA of 99.83%
- Conversion of positive to negative crossmatch occurred in 89.5% of transplants with varying occurrences of donor-specific antibodies that rebounded 3-14 days post-dose. Patient survival was 100% and graft survival was 88.9% with 38.9% BPAR with 2-19 days onset post-transplant.
- Overall, this enabled patients with high cPRA to successfully undergo transplant


- AMR occurred in 38% of patients within the first month. Comparing AMR+ to AMR-, allograft survival was 93% vs 77% and patient survival was 85% vs 94% with higher eGFR in the AMR-group (49 vs 61 ml/min/1.73m²)
- Confirms that imlifidase is an option for patients with significant immunologic barriers to undergo a successful kidney transplant


- A single-center prospective study with 13 highly sensitized (cPRA >95%) with well-tolerated results in all but one patient who presented with spondylodiscitis
- No difference in percent of lymphocyte subsets and Tfh cell subsets, but a significant increase in naïve B-cells, IL-6 levels, and sIL-6R; and significant decrease in plasmablasts
- Minimal effect on anti-HLA antibodies (class I and II)


- 10-year follow up of patients who received rituximab or underwent splenectomy
- Patient and graft survival was similar with rates between 94-95%, and similar AMR rates of 10.2% vs. 12.5%; of those who with AMR 3 lost their grafts (1 rituximab and 2 splenectomy)
- Patients who underwent splenectomy had higher rates of cytomegalovirus and incidences of late-onset neutropenia

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.


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.


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.


Prospective, open-label 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 (no desensitization).

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.


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.
- 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

- 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)

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

- 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)

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

- 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)

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

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

- 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%

- 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

- 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

- 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

- 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

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

- 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

- Web-based questionnaire distributed to nephrologists and transplant surgeons on immunosuppression management
- Response rate of 37% (104 responses from 283/283 programs) with thymoglobulin (84%) as the most common induction, 67% of responders using belatacept maintenance immunosuppression, and 72% with rapid steroid withdrawal protocols
- All responders use indication biopsies for T-cell mediated rejection and 99% for antibody mediated rejection with wide variations in occurrence of protocol and biomarker driven biopsy. Common treatments for TCMR included IV/PO steroids and PP/IVIG for ABMR. Use of rituximab, bortezomib, and eculizumab increased for recurrent ABMR compared to C4D+ ABMR. Harmonization of practice management for rejection is needed.

- Single-center study of 19 patients with biopsy-proven chronic active antibody-mediated rejection converted to belatacept with 90 day tacrolimus taper. Median time to conversion was 44 months (range 5-141 months).
- At average 29 month follow-up (IQR 16-46), 89% graft survival and 95% patient survival occurred
- Compared to a propensity-matched INSERM U970 registry, patients converted to belatacept had significant improvement in eGFR post-conversion (33.9 at baseline to 38.5 at 12 months), while control therapy had a decline in eGFR. No difference in biopsy results.

- Monthly tocilizumab was given to patients with AMR resistant to apheresis, rituximab, and IVIg with no difference in graft survival or renal function and overall did not alter the AMR course


- 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


- 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


- 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

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.


- 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


- 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 > 300, and C1q positivity associated with allograft loss


- 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

• 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.


• 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


• 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.


• 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.


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


• 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.

- 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)


- 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)


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


- 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)


- In-depth review of AMR and treatment modalities


- Updates from the 2011 Banff meeting, with a focus on refining criteria for AMR
- Systematic review of heterogeneous studies examining the treatment of acute AMR

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

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

- Case-based guide of the various crossmatching techniques

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

- Literature review of bortezomib for desensitization and treatment of AMR

- 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

- 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

- Evidence-based recommendations for the treatment of acute rejection
- 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)

- 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

- 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

- 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)

- 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)

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


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


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


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


- 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.


- 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


- 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


- 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.


- 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)


- 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


- 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


- UNOS database analysis of posttransplant lymphoproliferative disease (PTLD).
- PTLD occurrence in second kidney transplant was significantly higher in patients with a history of PTLD, but no difference in graft failure, all-cause mortality, and acute rejection


- Utilizing OPTN to assess retransplant after first graft loss due to BK virus associated nephropathy (BKVAN) compared to those without BKVAN. There was no difference in graft survival, acute rejection, and patient survival. Subgroup analysis showed that patients with graft loss due to BKVAN had better graft survival than patients with prior failure due to acute rejection and recurrent disease
- BKVAN should not be a contraindication to retransplant

Younger patients (18-64 years old) and older patients (≥65 years old) did not have significant differences in DGF, primary non-function, 1-year acute rejection or 5-year graft failure; 5-year mortality was higher in older recipients.


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 is similar to that of second graft recipients. Ahmed, 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.


- 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.


- 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


- Review article focusing on recurrence of disease after transplant as well as pathogenesis, biomolecular mechanisms, and therapy options
- Glomerulonephritis (GN) has changed from a minor contributor to graft loss to the 3rd most common cause of 10-year graft failure


- 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.


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


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

1.6.2 Focal Segmental Glomerulosclerosis

• Single-center, retrospective study of renal transplant recipients with primary diagnosis of FSGS. Patients at Scripps Center for Organ Transplantation (SCOT) using a rapid low-dose steroid withdrawal were compared to UNOS database of patients with FSGS.

• Graft failure and recipient death did not differ between SCOT SF cohort and UNOS SF cohort. There was a lower rate of FSGS recurrence in the SCOT cohort compared to previously published studies.

• Concluding that steroid avoidance and steroid-free protocols may not be detrimental when considering steroid adverse effects and toxicities.


• 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.


• 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.


• 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.


• 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


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


• 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.


• 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).


• 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


• 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.


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

1.6.5 IgA Nephropathy

- 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


- 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


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


- 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.


- 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.


- 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.

- 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).


- 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.


- 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


- 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


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

1.6.11 Polycystic kidney disease


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

- 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.

- 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.

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

- 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

- 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.

- 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.

- 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.

- 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.

- In patients with declining kidney function due to biopsy-proven chronic allograft nephropathy, calcineurin inhibitor dose was reduced or completely 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

- This review suggests that GLP-1RA are safe and effective in this patient population, but it is possible that higher rates of gastrointestinal events can occur. SGLT2i data is limited and even less than GLP-1RA and studies have shown high rates of discontinuation due to UTI adverse events and may be limited in the SOT population due to GFR dosing cut offs
- Insulin remains the first-line therapy for transplant patients with DM for the first 1-2 months and then could be considered for patients with other predisposing factors

- 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 metabolism and may reverse PTDM in the first year after converting to cyclosporine.


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


- 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.


- 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.


- 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 antimitabolite.

- 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.


- 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.


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