Long-term complications after kidney transplantation

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CLINICAL PRACTICE GUIDELINES

Post-operative Care of the Kidney Transplant Recipient

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Abstract

The 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline on the monitoring, management, and treatment of kidney transplant recipients is intended to assist the practitioner caring for adults and children after kidney transplantation. The guideline development process followed an evidence-based approach, and management recommendations are based on systematic reviews of relevant treatment trials. Critical appraisal of the quality of the evidence and the strength of recommendations followed the Grades of Recommendation Assessment, Development, and Evaluation (GRADE) approach. The guideline makes recommendations for immunosuppression, graft monitoring, as well as prevention and treatment of infection, cardiovascular disease, malignancy, and other complications that are common in kidney transplant recipients, including hematological and bone disorders. Limitations of the evidence, especially on the lack of definitive clinical outcome trials, are discussed and suggestions are provided for future research.

**Keywords:** Guideline; KDIGO; kidney transplant recipient care; immunosuppression; graft monitoring; infectious diseases; cardiovascular disease; malignancy; mineral and bone disorder; hematological complications; hyperuricemia; gout; growth; sexual function; fertility; mental health
Long-term complications after kidney transplantation

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Patient/Graft survival
Causes of Kidney Allograft Loss and Death in the United States, 2000-2010
Long-Term Outcomes Following Acute Rejection in Kidney Transplant Recipients: An ANZDATA Analysis

- Analysis of the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry, including all recipients of a primary kidney-only transplant between 1997-2011 (n=8376)
- The associations between AR during the first 6 months post transplant and cause-specific graft loss and death were determined using competing-risk survival analyses adjusted for baseline donor, recipient and transplant characteristics
Morphometric Age as a Predictor of Post Liver Transplant Survival

- Baseline morphometric characteristics of aging were determined using the CT scans of 348 liver transplant candidates versus 3313 control patients (trunk muscle size, muscle density, and vascular calcification).
- After adjusting for clinically relevant covariates, morphometric age was a significant predictor of:
  - 1 year mortality (p <0.001, OR = 1.05 95% CI: 1.03 - 1.07)
  - 5 year mortality (p <0.001, OR = 1.04 per morphometric year, 95% CI: 1.02 - 1.05)
- Importantly, after adjustment for morphometric age, chronologic age fell out of these risk models.
- Among the chronologically middle aged tercile, there was a profound difference in 1 and 5 year survival between patients who were “morphometrically” young compared to “morphometrically” old.
Trends in Kidney Transplant Outcomes in Older Adults

- 278,941 recipients (30,207 aged ≥65) studied from SRTR data between 1990-2011
- Mortality was obtained from Social Security Death Master File and graft loss through linkage with CMS.
- Older adults currently represent 17.6% of KT recipients, a 5-fold rise from 3.2% in 1990
- For older KT recipients, survival and death-censored graft survival improved over time among live donor and deceased donor recipients
Threatened Kidney Allograft: Use of mTOR-Inhibitor Increases All Cause Mortality

• Case-control study linking UNOS and ESRD databases
• All patients were on maintenance tacrolimus and MMF without steroids - based upon IF/TA on biopsy some converted tacrolimus to sirolimus
• A total of 497 recipients had different grades of IF/TA at the time of index biopsy. 221 (45%) patients were changed to sirolimus/MMF without steroids. There were no systematic differences in the baseline characteristics between the two groups, but significant differences in the primary and secondary outcomes in the two groups
• Sirolimus use increased all cause mortality and also death after graft loss in a multi-variable model (independent of baseline IF/TA gradient)
Cigarette Smoking in Living Kidney Donors and Graft Survival

- Retrospective single-institution review of 635 living kidney transplantations in an attempt to ascertain the effect of donor cigarette smoking and graft survival
- 26% of donors smoked within 1 year prior to their donor nephrectomy
- In Cox proportional hazard model, when compared to non-smokers, grafts harvested from donors who have smoked within one year of donor nephrectomy resulted in hazard-ratio for graft loss of 1.74 (p<0.001)
Treating chronic antibody-mediated rejection

• Effectiveness of Rituximab and IVIG for the treatment of chronic antibody-mediated rejection in kidney transplant recipients:
  – The combination of RTx and IVIg was effective for the delay of deterioration in CAMR, however the effect was limited (non-responders) in cases with massive proteinuria, more severe PTCs and previous acute rejection

• Eculizumab Therapy for Chronic Antibody-Mediated Injury in Kidney Transplantation: An Interim Assessment:
  – Interim assessment of transplant patients with de novo DSA and worsening renal function show an apparent stabilization in their renal function with eculizumab therapy
Donor-specific antibodies
Antibody-Mediated Injury Is the Major Cause of Late Kidney Allograft Failure

- Data reported from 469 cross-sectional patients (transplanted at any time with serum creat ≤ 2.0mg/dl on 1/1/06) in DeKAF study with up to 6 years follow up after biopsy
- Histology and DSA were determined from tissue and sera obtained at entry biopsy. Four groups were defined based on c4d and DSA status
- Among patients with late allograft dysfunction, evidence of antibody-mediated injury is common and negatively influences outcome. The impact of DSA alone may take longer to manifest, but the ultimate result is similar with or without c4d at initial biopsy
- Antibody-mediated injury is the major cause of late kidney allograft failure.
Development of De Novo Anti-HLA Abs in Kidney Transplant Recipients: Final Analysis of the NIH CTOT02 Study (1)

- The NIH CTOT02 is the first large multi-center prospective study to examine the causes and effects of development of post-transplant de novo anti-HLA Ab in unsensitized kidney transplant recipients.
- Data were analyzed for 653 subjects enrolled in the screening phase of the study from 17 centers, who were followed for development of de novo HLA-Ab for up to 60 months post-transplant.
- 79 (12%) subjects developed de novo HLA-Ab.
- The mean age of HLA-Ab positive subjects was significantly younger, 36.8 vs 43.2 years (p=0.001)
- Use of anti-IL2R Ab as induction therapy was independently protective against development of anti-HLA Abs (p=0.002)
Development of De Novo Anti-HLA Abs in Kidney Transplant Recipients: Final Analysis of the NIH CTOT02 Study (2)

- Anti-HLA Ab positive subjects were significantly more likely to develop rejection (22.8% vs 5.4%, p<0.001), with in-vitro complement binding anti-HLA Ab being more highly associated with rejection
- Samples from 74 of 79 anti-HLA positive subjects were available for in vitro C1q binding studies: 36 (48.6%) were C1q positive and 38 (51.4%) were C1q negative, with complement binding Ab being significantly more likely to be directed against donor specific antigens (p=0.007), and associated with rejection (33.3% vs 10.5 %, p=0.024)
- Despite this, and in contradiction to previously reported retrospective studies, there was no difference in allograft survival in subjects who developed anti-HLA Abs
Post allograft failure
Immunosuppression after Renal Allograft Failure: A Survey of US Practices

• To document current practices in the US, we emailed a questionnaire to medical and surgical transplant directors as identified by the United Network for Organ Sharing.
• Emails were sent to 221 programs, of which 93 (42.1%) responded
• 24.7% reported using a standard protocol, with the majority reporting that practices are physician-dependent
• First to wean: MMF/AZA (57.6%), CNI (38.0%),
• Next to wean: MMF/AZA (35.5%), CNI (55.9%), SIRO (2.2%), steroids (6.5%)
• What do you leave on permanent; MMF/AZA (5.4%), CNI (5.4%), steroids (21.5%), none (71.0%)
• Respondents most commonly said they performed graft nephrectomy only if there are signs and symptoms of rejection (47.3%) or if signs and symptoms of rejection fail to respond to steroids (34.4%)
Cardiovascular disease
Cardiopulmonary Exercise Testing (CPX) for Cardiac Risk Assessment Prior to Kidney Transplantation

- Algorithm for screening before kidney tx in high cardiac risk (1 or more criteria: diabetes mellitus (DM), coronary artery disease (CAD), age >50 yrs) patients:
  - If CPX results indicate VO2 <17 mL/kg/min (~METS <5.5), NIST (stress MIBI) is performed
  - If VO2 ≥17 mL/kg/min, no further testing unless prior angioplasty or CABG wherein NIST is performed.

- Lower VO2 correlated to longer hospital stay post-tx (4.4 versus 3.1 days respectively, p=0.03)
- No cardiac events, deaths or graft losses (n=29)
- Potential cost saving (MIBI costs: $2000, CPX: $200) and avoidance of radiation exposure from the MIBI
Cardiovascular risk factors
Comparative Ability of Different Metabolic Syndrome Definitions To Predict Major Adverse Cardiovascular Events after Kidney Transplantation

• The predictive ability of each definition of metabolic syndrome (IDF 2006, WHO 1999, NCEP 2001, updated NCEP 2004) for major adverse cardiac events (MACE) after kidney transplantation has not been compared.

• After excluding patients with type 1 diabetes (N=30), a retrospective analysis of 1182 adult single-organ kidney transplant recipients performed (1998-2010)

• Among metabolic syndrome definitions, the WHO definition is the only predictor of MACE in kidney allograft recipients (MACE rate per 100 patient years 2.53 versus 1.55, p=0.019)
Infections
What Is the Best Treatment for BK Viremia after Kidney Transplantation: Results of a 5-Year Screening Study

- 609 kidney or kidney/pancreas recipients from January 2007 to June 2011 prospectively screened for BK viremia.
  - By 1-year, 130 (21.3%) had at least one positive BKV PCR.
- Patients classified with BK viremia according to the treatment received into 5 groups:
  - Observation Alone n=45;
  - Decrease (30-50%) or Stop Immunosuppression (IS) n=43;
  - Decrease or Stop IS + Cipro n=14;
  - Decrease or Stop IS + Leflunomide n=18;
  - Decrease or Stop IS + Cipro + leflunomide n=11.
- BK clearance associated with:
  - Lower BK viral loads at first detection and peak
  - Absence of doubling compared to first detection
  - Female gender
  - CMV negative serostatus
- No evidence for adding leflunomide or cipro to 30-50% reduction in overall IS.
Risk Factors for Graft Loss Due to BK Nephropathy: A Paired Kidney Analysis

• Using SRTR data from 1987-2011, 460 deceased-donor BK transplant failures (cases) identified and linked to their mate kidney (controls)

• The final study population included n = 419 BK pairs:
  – Excluded: both mate kidneys failing due to BK (n=2) and if control kidney had BK infection (n=39)

• Donor factors were found to play a minor role in transplant failure due to BK

• This unique paired kidney analysis also confirms the following with risk for transplant failure due to BK:
  – Male gender
  – Treatment with tacrolimus as opposed to cyclosporine
  – Acute rejection in the first post transplant year
TCMR Is Underdiagnosed in BK Virus Nephropathy: A Tale of 2 Populations

- 703 biopsies for clinical indication, including 25 with BKN, 67 with TCMR but no BKN studied for histologic and molecular phenotyping
- Typical TCMR is common in BKN but is often not diagnosed
- BKN with TCMR features manifests worse function than BK alone because it has two diseases impairing function
- A molecular classifier that was built to distinguish biopsies with TCMR from BKN failed
Transplant pathology
Transplant pathology - guide for dummies

1. **C4d deposition is bad news**
   - But not always bad news

2. **Glomerulitis and peritubular capillaritis are bad news**
   - Maybe more significant than C4d to diagnose AMR
   - Maybe additive value to C4d alone
   - Or maybe no added value if C4d negative

3. **Correlating DSA with histopathological evidence of antibody-mediated injury remains difficult**

4. **Isolated 'v' lesions are still puzzling**

5. **BKVAN and T-cell mediated rejections look a wee bit similar and dissimilar at the same time**

6. **The molecular microscope is the new technology (but we still don't know how to use it and not sure if it is any better than light microscopy)**

7. **Concordance between pathologists is poor for interpretation of transplant histopathology**
Malignancy
Cohort Study of Solid Organ Transplant Recipients Who Develop Malignancy: Risk of Subsequent Malignancy on mTOR vs. Non-mTOR Regimens

• 12-year retrospective cohort study to compare the risk of second malignancy in those exposed to mTOR-I (n=144) versus those not exposed to mTOR-I (n=48)

• Most common second malignancy was non-melanoma skin cancer (72%)

• Mean cumulative dose of mTOR-I was higher in those who did not form a second malignancy (p<0.001)

• Furthermore, any use of mTOR-I after the diagnosis of a first malignancy was associated with a lower risk of a second malignancy regardless of cumulative dose of other immunosuppressive drugs (HR 0.37 [CI 0.24-0.57], p<0.001)
Addition of Anti-CMV Ig to Routine CMV Prophylaxis in EBV High Risk Kidney Transplant Recipients Is Associated with Reduced PTLD Incidence

• Data was collected on 1256 renal txp pts from 1998-2012
• All pts received CMV prophylaxis with either valgancyclovir, gancyclovir, or acyclovir
• 47 EBV high risk pts (ie, donor EBV seropositive to recipient EBV seronegative pts) were analysed in 2 groups:
  – Pts receiving anti-CMV Ig (n=25) - GROUP 1
  – Pts not receiving anti-CMV Ig (n=22) - GROUP 2
• Anti-CMV Ig dosing was 100mg/kg at 1, 2, 4, 6, and 8 weeks then 50mg/kg at 12 and 16 weeks
• PTLD rate was 0.0% versus 23.0% between Group 1 versus Group 2 (p=0.01)
Maintaining a Calcineurin-Inhibitor after the Diagnosis of PTLD Is Safe and Improves Renal Graft Survival

- Retrospective review of 101 cases of PTLD to identify risk factors associated with renal graft loss
- During follow-up (median: 35 months, range: 1-208) 39 patients died (38.6%) and the rate of death-censored graft loss was 20.8%
- Independent risk factors for graft loss were:
  - eGFR<30ml/min/1.73m2 at PTLD diagnosis
  - Biopsy-proven acute rejection episode following RIS
  - Absence of a CNI in maintenance immunosuppression
- Neither type of PTLD, nor the chemotherapy regimen, was predictive of allograft failure
- Histological analysis of graft biopsies revealed that maintaining a CNI at reduced dose after the diagnosis of PTLD reduces the risk of humoral rejection.
- CNI maintenance was neither associated with a higher mortality, nor with a worse progression free survival.
Risk of Recurrence of Pre-Existing Cancer in Organ Recipients

- Data linked between National Transplant Registry (1985-2010) in the West Midlands region with the regional Cancer Registry
- The study cohort of 4835 recipients included 3321 (69%) kidney, 821 (17%) liver, 495 (10%) heart and 198 (4%) lung recipients.
- A history of cancer was noted in 64 (1.32%) recipients
  - 5 recipients developed cancer recurrence within 10 years of transplantation.
- All five recipients with recurrence had been cancer-free for less than five years pre-transplant
- There were no cases of recurrence of cancer in 59 recipients of whom, at transplant, 39 had been cancer-free for more than five years. Melanoma recurred in 3 of the 4 patients with a previous diagnosis; the other 2 cancers which recurred were leiomyosarcoma and testicular cancer.
- In all 5 cases, the recipients died as a direct consequence of recurrent cancer
Occurrence of Non-Melanoma Skin Cancer Predicts Risk of Subsequent Solid Organ Cancer

• Incidence of solid-organ cancer after kidney transplants performed in Australia or New Zealand from 1975-2011 (n=18,031) was analysed.

• Crude hazard ratio for the occurrence of a solid organ malignancy after NMSC was 1.69 [1.53-1.86]; adjusted for age, gender, living vs deceased donor and year of transplant this was 1.22 [1.11-1.36], p<0.001.

• Among kidney transplant recipients, there is an increased risk of solid organ cancer after the occurrence of a NMSC (independent of other risk factors for cancer such as age, year of transplantation, anti-CD3 use etc.)
Pregnancy
Pregnancy Outcomes in Solid Organ Transplant Recipients with a Switch from a Mycophenolic Acid Product to Azathioprine Prior to Conception

• Switching from mycophenolic acid product (MPA) to azathioprine (AZA) >6 wks prior to conception.
• 69 recipients (71 pregnancies, 74 outcomes) switched their regimen from MPA to AZA in anticipation of conceiving. Of those, 56 recipients conceived 58 pregnancies after switching
• Pregnancy outcomes included 51 live births (88%), 4 spontaneous abortions (7%), 2 stillbirths, and 1 therapeutic abortion
• At last follow-up, all children were reported healthy and developing well (two born with minor birth defects)
• Half of the recipients resumed MPA postpartum
• At last maternal follow-up, 2 (4%) kidney recipients reported graft loss within 2 yrs of delivery (remained on AZA), 1 PK recipient lost P function during pregnancy and the remaining 53 recipients reported adequate graft function.
Pregnancy Outcomes in Solid Organ Transplant Recipients with Exposure to Sirolimus

- 26 transplant recipients (16 kidney, 5 liver, 4 heart, and 1 pancreas-kidney) reporting 30 pregnancies with exposure to sirolimus.
- There were 19 live births and 11 spontaneous abortions. Four of the pregnancies were reported being planned, while 26 were reported as an unplanned pregnancy.
- Sirolimus was continued throughout the pregnancy in 11 cases, discontinued during pregnancy in 18, and started in the third trimester during 1 pregnancy. Two kidney recipients had rejection during pregnancy.
- Among the 19 live births the incidence of prematurity was 47%. Two infants had birth defects: in one infant there were multiple malformations including cleft lip and palate and microtia (late exposure to sirolimus and early exposure to MPA) and Tetralogy of Fallot in the other. The remaining 17 children were reported healthy and developing well.
Renal bone disease
Impact of Vitamin D, Bisphosphonate, and Combination Therapy on Bone Mineral Density in Kidney Transplant Patients (1)

- 182 renal transplant recipients were retrospectively analysed:
  - Group 1 (n=73) - received neither vitamin D nor bisphosphonate after transplantation
  - Group 2 (n=40) - received calcium + vit D
  - Group 3 (n=18) - received bisphosphonate
  - Group 4 (n=51) - received both calcium/vit D and bisphosphonate

- Bone mineral density (BMD) was evaluated by dual-energy X-ray absorptiometry at baseline and 1 year after transplant

- At 1 year after transplantation, T-scores of the femur neck and entire femur significantly decreased in group 1 [\(-0.23 \, 0.65 \) (\(P=0.004\)) and \(-0.21 \, 0.74 \) (\(P=0.018\)), respectively], whereas the T-score of the lumbar spine significantly increased in group 4 (\(0.27 \, 0.79, P=0.020\)).
Impact of Vitamin D, Bisphosphonate, and Combination Therapy on Bone Mineral Density in Kidney Transplant Patients (2)

• In a multivariate analysis adjusted by age, gender, body mass index, dialysis duration, diabetes, calcineurin inhibitors, eGFR, and persistent hyperparathyroidism, both group 2 and group 4 showed protective effects on BMD reduction (OR 0.165, 95% CI 0.032-0.845, P=0.031 and OR 0.169, CI 0.045-0.626, P=0.008, respectively)

• Group 3 did not show a protective effect (OR 0.777, CI 0.198-3.054, P=0.718) because the incidence of persistent hyperparathyroidism after transplant was significantly higher (50.0%) than for the other groups (P<0.001)

• The incidence of bone fractures did not differ among the groups
Transplant dermatology
Transplant Dermatology Is an Essential Part of Transplant Care: Report of First Year Experience

- Single centre first year experience with a new transplant dermatology clinic
- A total of 100 newly referred transplant patients were evaluated; 58 men and 42 women (mean age 52 years)
- Among the 100 patients there were 40 distinct dermatologic diagnoses excluding nevi and lentigines.
- These included 22% who had either a malignant (13%) or a pre-malignant (9%) diagnosis;
  - basal cell carcinoma (5)
  - squamous cell carcinoma or squamous cell carcinoma in-situ (2)
  - Both BCC and SCC/SCCIS (6).
  - No melanomas were identified
  - Pre-malignant diagnoses included actinic keratosis, porokeratosis and atypical intraepidermal melanocytic proliferation
- Of the 13 patients with skin cancer, only 2 reported a known history of skin cancer
Long-term donor outcomes
Renal Outcomes in Prediabetic Living Kidney Donors Are Very Similar to Normoglycemic Donors at 10 Years Post-Donation

- Single centre retrospective study of living kidney donors from 1996-2007 with serum glucose >100 mg/dl (impaired fasting glucose or IFG)
- Donors with normal fasting glucose matched for age, sex and year of donation were identified as controls
- 45 prediabetic donors and 45 normal controls were enrolled
- At baseline both groups similar apart from pre-diabetics had higher fasting glucose (109 versus 87, p=0.001) and BMI (28 versus 25, p=0.022)
- eGFR, ACR, cardio-metabolic markers were all equivalent
  - Ten years post donation, incidence of new-onset diabetes was (15.6% versus 2.2%, p=0.059)
What Is the Implication of Pre-Donation Weight Loss to the Post-Donation Weight and Outcome of Living Donors

- To study whether obese potential donors are at greater risk of regaining the weight they lost post donation
- Median BMI at preassessment was 26.8 with 25% of patients having a BMI over 30.3 and 14% a BMI over 32.
- Patients with BMI at preassessment of greater than 30 lost 4.5% of their weight to donate and their loss in weight at donation was statistically different (from BMI 30.5 to a BMI of 27.7, p=0.005) from the rest of the patients
- Patients weight change at 1 and 2 years is inversely related to the change of weight between preassessment and donation (p=0.002) and is independent of BMI group at preassessment and donation, gender or age.
- Obese donors lose the weight required to donate but some of it is regained with adverse impact on systolic and diastolic blood pressure and serum creatinine
Long-Term Risk of ESRD Attributable to Live Kidney Donation: Matching with Healthy Non-Donors (1)

• No study has compared ESRD incidence in donors to ESRD incidence in comparable non-donors. ESRD risk attributable to donation is unknown.
• Cohort of 96,217 live kidney donors (reported to OPTN between 1994-2011) was matched to healthy non-donor controls drawn from the NHANES study, using an incrementally expanding radius matching algorithm previously published (JAMA 2010) based on age, gender, race, education, BMI, systolic blood pressure, and smoking history.
• Both donors and controls linked to CMS data to obtain ESRD outcomes. Kaplan-Meier curves used to compare 15-year ESRD incidence, overall and separately among racial/ethnic subgroups. A novel bootstrap method was used to assess statistical significance.
Long-Term Risk of ESRD Attributable to Live Kidney Donation: Matching with Healthy Non-Donors (2)

- ESRD incidence at 15 years was $8\times$ higher for live kidney donors (0.31%) than for healthy matched controls (0.04%) ($p<0.05$)
- Higher incidence of ESRD was observed among following donors:
  - Black > White
  - Old > Young
  - Male > Female
- Fifteen-year incidence was less than one percent among all racial/ethnic subgroups.
- Live kidney donors had higher rates of ESRD than matched controls, overall and across racial/ethnic subgroups. However, absolute risk of ESRD within fifteen years of donation is low in all subgroups.