Late Post-Transplant Medical Complications

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• Clinical focus: Glomerular disease recurrence, chronic rejection, antibody-mediated rejection
• Research focus: Immune regulation
Disclosure of Financial Relationships

Leonardo V. Riella, MD, PhD

Investigator-initiated research with Bristol Meyers Squibb, CareDx and Visterra.
Goals of the talk

What are the most common complications late post-transplantation?

What are the underlying mechanisms involved in these complications?

What are transplant-specific treatment options?
45-year old male with ESRD from polycystic kidney disease received a living donor kidney transplant 2 years prior. He was evaluated in the post-tx clinic today and has the following question: “What is the most likely cause of death in a patient like me”?

A. Malignancy
B. Infection
C. Stroke
D. Cardiovascular disease
E. Trauma
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B. Infection
C. Stroke
D. Cardiovascular disease
E. Trauma
Causes of death with a functioning graft

USRDS data (2004-2008)

- CV disease
- Infection
- Malignancy

Percentage

USRDS data (2004-2008)
Cardiovascular mortality by age group

Adapted from Jardine AG, et al. Lancet 2011;378:1419
Risk Factors for CV Disease after Kidney Transplantation

*Traditional CV risk factors are poor predictors in the transplant population
Heterogenous Heart Disease after Kidney Transplantation

• Myocardial infarction is associated with dyslipidemia, age and diabetes

• Cardiac death is associated with severe hypertension, left ventricular hypertrophy and poor graft function.

To improve CV outcomes, we must manage complications aggressively and reduce immunosuppression when possible. Consider ASA and statin in high CV risk patients.
58-year old Hispanic male with ESRD from MPGN who received a deceased kidney transplant 2 years prior. His post-op course was uncomplicated. He is currently on tacrolimus 6mg BID, mycophenolate 750mg BID, prednisone 5mg daily. His body mass index is 29. He was noted to have a fasting serum glucose of 120 mg/dL on a routine clinic visit. Which ONE of the following is the MOST appropriate next step in management

A. Convert from tacrolimus to cyclosporine
B. Stop prednisone
C. Loose weight with diet and exercise
D. Start metformin
E. Start insulin therapy
Case 2

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Prevalence of Transplant-Associated Hyperglycemia (TAH)

- **Post-tx DM**: 21%
- **Normal**: 57%
- **Pre-diabetes**: 22%

Oral glucose tolerance test

*n=606 kidney recipients without prior DM 1 year after transplantation*

Adapted from Porrini et al. NDT 2016
Independent Effects of PTDM on Graft and Patient Survival

CV Events and Transplant-Associated Hyperglycemia

- Normal fasting glucose
- Impaired fasting glucose
- Post-tx DM

Sumrani et al. Transp 1991;343-47
Pathogenesis of Hyperglycemia

**Transplant-Associated Hyperglycemia**

- **↑ Hepatic Gluconeogenesis**
- **↓ Insulin Secretion**
- **↓ Insulin Sensitivity**

**Investigation:** check for fasting serum glucose and HbA1c (not reliable early after transplant).

*Riella LV. Kidney Transplant iBook 2019*
Effects of Calcineurin Inhibitors on Pancreatic β Islet Cells

Control | Cyclosporine | Tacrolimus

Insulin Staining (black)

Effect of Steroids and Tacrolimus on Glucose Metabolism

- Stimulated insulin production
- Insulin sensitivity index
- Insulin resistance

Randomized trial of different induction therapies with or without steroid withdrawal
~200 patients on each group

Steroid withdrawal is associated with lower incidence of post-transplant DM

* All groups received high-dose steroids early after tx

Thomusch et al. Lancet 2016
Management of Post-tx DM - Stepwise Approach

Lifestyle changes (diet, exercise and weight loss) - goal HbA1c<7.5%

- Oral Hypoglycemic Agents [e.g. metformin, SGLT2 inhibitors, glipizide or DPP-4 inhibitors (sitagliptin, or vildagliptin)]

+ dulaglutide glucagon-like peptide 1 receptor agonist (GLP-1 RA) SC weekly

Decrease immunosuppression if possible

Insulin Therapy
MGH Guidelines for SGLT2 inhibitors in kidney transplant recipients with diabetes

Consider as add-on therapy in diabetic kidney recipients already on metformin

Requirements: >1 year post-transplant, eGFR>30ml/min, on stable immunosuppression and no history of recurrent UTIs.

Options: Empagliflozin 10mg daily, Canagliflozin 100mg daily

Monitor
- blood pressure daily and if symptoms of lightheadedness/dizziness
- blood test with creatinine/eGFR at 2, 4 and 8 weeks after initiation.

For patients with eGFR<30ml/min, consider dulaglutide [glucagon-like peptide 1 receptor agonist (GLP-1 RA)]
Randomized single center study of 44 kidney recipients with DM
**Empagliflozin 10mg daily vs placebo for 24 weeks**
Inclusion: >1 year post-transplant, eGFR>30ml/min and stable immunosuppression

**Outcomes:**
Small reduction in Hb1ac, Lower weight (-2.5kg), Stable eGFR at 24w

Empagliflozin group
Transient reduction in eGFR at 8w
1 urosepsis (history of prior UTIs)
Reduced glucose lowering if eGFR<30

Halden et al. Diabetes Care 2019
Death with a functioning allograft is a major cause of long-term graft loss;

Mortality after tx: CV>infection>malignancy

Tx-specific CV risk factors: dialysis time pre-tx, poor allograft function, metabolic disorders due to IS drugs.

Tx-associated hyperglycemia affects most kidney recipients and is associated with worse graft function and death.

Multifactorial: immunosuppressive drugs (tacrolimus> cyclosporine), weight gain

Metformin: risk of lactic acidosis in the setting of renal failure. FDA update: adjust dose if GFR 30-45 ml/min; contraindicated <30 ml/min.
Prevalence of HTN Post-Transplant

1 year after kidney transplantation

SBP>140: 65%
SBP≤140: 35%

n=3,571

Adapted from Opelz et al. AJT 2005; 5:2725-2731
CNI mediated vasoconstriction

Afferent arteriole vasoconstricted

Normal glomerulus

After CNI exposure

Riella LV. Kidney Transplant eBook 2019
Transplant Renal Artery Stenosis

- Refractory hypertension at 3-24 months after surgery ± elevation of creatinine
- Deceased donor > Living donor;
- Diagnosis: arteriography (gold-standard); US Doppler (operator-dependent); MRA or CTA
- Treatment:
  Percutaneous intervention;
  success rate up to 94% with ~10% recurrence.

Riella LV. Kidney Transplant iBook 2019
Management of Post-Transplant HTN

- Goal BP <140/90 mmHg
- Consider reduction of CNI dose if possible
- First choice: calcium channel blocker (interaction)
- Diuretics (HCTZ); Beta-blocker (labetolol, metoprolol)
- ACEI/ARB (stable course)
  - ↓ proteinuria but also ↓GFR, ↓Hb, ↑Potassium
  - potential benefits in diabetics, q with proteinuria or CV disease
  - No clear patient or graft survival advantage.

Cross et al. Cochrane Dat Sys Rev 2009
75-year old Caucasian male with ESRD from lithium toxicity 20 years prior presents to outpatient clinic with 20 pound weight loss and night sweats. His post-transplant course has been unremarkable and he takes tacrolimus 4 mg BID, mycophenolate 1 g BID, prednisone 5mg daily and amlodipine 10 mg daily.

On exam, he is afebrile, BP 115/90, HR 90. Lungs are clear to auscultation. Abdomen noticeable for palpable enlarged polycystic kidneys and tender allograft. Palpable enlarged femoral lymph nodes bilaterally. Creatinine is at baseline 1.8 mg/dL. Which ONE of the following is the MOST appropriate next step in management?

A) Kidney biopsy
B) PET-CT scan
C) Chest X-Ray
D) Abdominal X-Ray
E) Abdominal MRI
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E) Abdominal MRI
Common Post-Transplant Malignancies

EBV
- Lymphoma (PTLD)

HHV-8
- Kaposi Sarcoma

Skin cancer

Kidney cancer

Engels et al. JAMA 2011; Van Leeuwen et al. BMJ 2010
Pathogenesis of Malignancy Post-Transplant

- UV light
- Smoking
- DNA damage (e.g. p53 mutation)
- mTor inhibitors
- DNA repair
- Aging
- CSA/AZA

Uncontrolled proliferation of tumor cells

Immunosurveillance
- TGF-β, IL-10

Immunosuppressive drugs
- T-cell depleting therapy
- Pretransplant dialysis

Production growth factors/
- anti-apoptotic proteins

Oncogenic Viral Infection
- Virus

Aging CSA/AZA DNA repair DNA damage (e.g. p53 mutation) Immunosurveillance mTor inhibitors UV light Smoking

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Aging CSA/AZA DNA repair DNA damage (e.g. p53 mutation) Immunosurveillance mTor inhibitors UV light Smoking
Post-Transplant Lymphoproliferative Disease (PTLD)

- Most common type: non-Hodgkin Lymphoma
- Peak incidence on first year after transplant
- Strong association with EBV infection (monitor VL)
- Major risk factors: EBV negative status, high degree of immunosuppression (rejection treatment) and CMV co-infection
- Treatment:
  - reduction of immunosuppression,
  - anti-CD20 therapy (rituximab) and/or chemotherapy

Nourse et al. Am J Transplant. 2011
Dhamidhark VR. Am J Transplant. 2017
<table>
<thead>
<tr>
<th>Infectious Agent</th>
<th>Viral-Associated Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein-Barr Virus</td>
<td>Lymphoproliferative Disorder</td>
</tr>
<tr>
<td>Hepatitis B Virus, Hepatitis C Virus</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Human Herpes Virus 8</td>
<td>Kaposi sarcoma</td>
</tr>
<tr>
<td>Human Papillomavirus</td>
<td>Cancer of the cervix, vagina, penis, anus, tongue, mouth, oropharynx</td>
</tr>
<tr>
<td>Merkel Cell Polyomavirus</td>
<td>Merkel Cell Carcinoma</td>
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</tbody>
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Increase risk of cancers related to ESRD (kidney cancer, thyroid cancer, urinary tract cancer)
Risk of breast and prostate cancers are not increased post-transplant.
mTOR inhibitors and Cancer

- Conversion has shown favorable results in case of Kaposi sarcoma, renal cell carcinoma and skin cancers.
- **Mechanism**: anti-proliferative and anti-angiogenic properties
- **Major limitation: side effect profile**
  - proteinuria, edema
  - anemia
  - hypertriglyceridemia
  - diarrhea, mouth ulcers
  - poor wound healing
  - pneumonitis

**Contraindications:**
- GFR<40 ml/min,
- proteinuria >500 mg/day

Holdaas et al. Transplantation 2011;92:410
mTOR inhibitor in Secondary Skin Cancer Prevention

• Multicenter trial (n=120): pts on CNI and at least 1 SCC were randomized 1:1 to sirolimus or CNI continuation.
• Primary end-point: survival free of SCC at 2 years

Relative risk: 0.56 (0.32-0.98)

60 serious adverse event mTORi (lung,GI)
vs 14 in CNI group
23% discontinuation rate mTORi
Graft function stable on both groups

A multi-center study on safety and efficacy of immune checkpoint inhibitors in cancer patients with kidney transplant

Retrospective cohort study (2010-2020)

- International Multi-center (23 institutions)
- Kidney transplant recipients (n=69)
- ICI therapy for advanced cancer (aPD-1, aPD-L1, aCTLA-4)

Safety
- Acute rejection: 42%
- Time to rejection: 24 days
- Graft loss: 65% of rejection

Efficacy: Tumor response to ICI therapy (complete response + partial response)
- Skin squamous cell carcinoma (n=24): 36%
- Melanoma (n=22): 40%

CONCLUSION:
Immune checkpoint inhibitors are associated with high acute rejection rate but result in reasonable tumor response.
• Hypertension: correlate with CNI dose; exclude transp. RAS if severe/refractory HTN;
• First-line agent to treat HTN post-transplant is amlodipine.
• Most common cancers after tx: non-melanoma skin cancer, Kaposi sarcoma, PTLD, RCC

• Strong association with viral infection and degree of immunosuppression
• mTOR inhibitors are protective against cancer but have many side effects (proteinuria, edema, hyperlipidemia, poor wound healing)
• Immune checkpoint inhibitors use is associated with rejection in ~40% of kidney recipients.
Drug-Drug Interactions

- **MMF**: absorption affected by antacids (magnesium hydroxide, aluminum, PPI) or calcium supplements.
- Diarrhea increases CNI levels
- Increase CNI levels (via P450):
  - non-dihydropyridine calcium channel blockers (e.g., diltiazem, verapamil)
  - antifungals (all azole derivatives)
  - macrolide antibiotics (especially clarithromycin, erythromycin)
Adjustment of Immunosuppression

Depending on the immunological risk of the individual patient:

- Number of HLA mismatches; living-related or not.
- Presence of pre-formed anti-HLA antibodies (sensitized)
- Prior rejection episode
- History of cancer
- History of infections
- Primary cause of kidney disease (auto-immune?)

Month 1  Months 2-6  > 6 Months


Thank You!

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Kidney Transplant eBook (Apple store)
Abbreviations

ACEI = ACE inhibitor
AVN = avascular necrosis
AZA = azathioprine
CCB = calcium channel blocker
CMV = cytomegalovirus
CNI = calcineurin inhibitors
CSA = cyclosporine
CV = cardiovascular
EBV = Epstein Bar Virus
FGF-23 = fibroblast growth factor 23
HTN = hypertension
IS = immunosuppression
MMF = mycophenolate mofetil
NODAT = new onset diabetes after tx
PTH = parathyroid hormone
RAS = renal artery stenosis
RCC = renal cell carcinoma
TAH = transplant-associated hyperglycemia
Tx = transplantation
VL = viral load