Renal Dysfunction After Non-Renal Solid Organ Transplantation

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I have **NO** financial relationships to disclose

- and -

I **will not** discuss off label use and/or investigational use in my presentation.
Objectives

• Review the definition and epidemiology of “kidney disease” in the general and transplant populations

• Describe the general and organ-specific risk factors associated with peri- and post-transplant acute kidney injury & chronic kidney disease

• Identify some of the complicating factors associated with kidney disease including “calcineurin inhibitor (CNI)-nephrotoxicity”

• Describe preventive & management strategies for kidney disease after solid organ transplantation
Why This is a Problem??

- Chronic Kidney Disease (CKD) is an increasingly recognized **long-term complication** of solid organ transplantation (SOT).
- The 5-year risk of CKD after transplantation of a non-renal organ ranges from 7 to 21%*
- CKD in the SOT population is associated with a **4- to 5-fold increased risk of death**.
- CKD occurs despite advancements in immunosuppression and peri-operative management.
- CKD occurs much more frequently than other complications — such as post-transplantation cancer!

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*Ojo et al. N Engl J Med 2003;349:931*
Definition of CKD
Definition of CKD
3 Key Components

• Anatomical or structural component:
  • Parenchymal disease: abnormalities in the composition of urine or histology
  • Decreased nephron mass: solitary kidneys, small kidneys, PKD, etc.

• Temporal component: >3 months of abnormality

• Functional component: estimated GFR <60 ml/min/1.73 m², with or without kidney damage

AJKD 2002
# GFR Estimation Drives CKD Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>eGFR (ml/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or ↓ GFR</td>
<td>&gt;90</td>
</tr>
<tr>
<td>2</td>
<td>Mild ↓GFR</td>
<td>60-89*</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 or dialysis</td>
</tr>
</tbody>
</table>

* may be normal for age

AJKD 2002

<table>
<thead>
<tr>
<th>GFR (mL/min/1.73 m²)</th>
<th>N*</th>
<th>Prevalence (95% CI)</th>
<th>Millions of Individuals (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90+</td>
<td>10,183</td>
<td>64% (63–66)</td>
<td>114 (106–122)</td>
</tr>
<tr>
<td>60–89</td>
<td>4,404</td>
<td>31% (30–33)</td>
<td>55.3 (50–61)</td>
</tr>
<tr>
<td>30–59</td>
<td>961</td>
<td>4.3% (3.8–4.7)</td>
<td>7.6 (6.5–8.6)</td>
</tr>
<tr>
<td>15–29</td>
<td>52</td>
<td>0.2% (0.1–0.3)</td>
<td>0.4 (0.2–0.5)</td>
</tr>
</tbody>
</table>

GFR estimated from serum creatinine using MDRD Study equation based on age, gender, race and calibration for serum creatinine.

*N is based on number of individuals in each listed GFR range in NHANES III, 1988–1994. Prevalence and number of individuals estimated by extrapolation to population of US adults age ≥20 (N = 177 million). Based on one-time assessment of estimated GFR.

Coresh et al, *AJKD* 2002
Why Glomerular Filtration Rate (GFR)?

- GFR is considered the best overall index of kidney function
- A decrease in the GFR is related to severity of kidney disease
- A decrease in GFR is independently associated with increased risk of mortality
### Creatinine-Based Estimation Equations

<table>
<thead>
<tr>
<th></th>
<th>Cockcroft-Gault</th>
<th>MDRD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population/Year</strong></td>
<td>Canadian VA/1976</td>
<td>Multicenter/USA/1999</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Inpatients</td>
<td>Outpatients with CKD</td>
</tr>
<tr>
<td><strong>Reference method</strong></td>
<td><em>Creatinine clearance</em></td>
<td><em>125-I-iothalamate</em></td>
</tr>
<tr>
<td><strong>Mean CrCl/GFR</strong></td>
<td>73 ml/min</td>
<td>40 ml/min/1.73 m²</td>
</tr>
<tr>
<td><strong>Variables in equation</strong></td>
<td>Age, gender, <strong>weight</strong></td>
<td>Age, gender, <strong>race</strong></td>
</tr>
<tr>
<td><strong>Mean age</strong></td>
<td>? (range 18-92)</td>
<td>51</td>
</tr>
<tr>
<td><strong>Percent females</strong></td>
<td>4%</td>
<td>40%</td>
</tr>
<tr>
<td><strong>AA race</strong></td>
<td>?</td>
<td>12%</td>
</tr>
<tr>
<td><strong>Adjusted for BSA</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
**GFR: Mathematical Equations!**

- **Cockcroft-Gault** = \([(140 - \text{age}) \times \text{Wt} / (72 \times \text{SCr})] \times 0.85\) if female = \(\text{ml/min}\) (not adjusted for BSA)

- **Nankivell** = \([6700 / (\text{SCr} \times 88.4)] + (\text{wt}/4) + (\text{urea}/2) - (100/\text{ht}^2) + 35\) if male or 25 if female

- **Abbreviated MDRD** = \(186 \times \text{SCr}^{-1.154} \times \text{Age}^{-0.203} \times 0.742\) if female \(\times 1.212\) if AA = \(\text{ml/min}/1.73 \text{ m}^2\)

- **CKD-EPI** = \(141 \times \min(\text{Scr}/k,1) \alpha \times \max(\text{Scr}/k,1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018\) [if female] \(\times 1.159\) [if black]

Better Estimation of GFR by the MDRD equation

B

Cockcroft-Gault

C

7-var MDRD

Levey et al, Ann Intern Med 1999
MDRD Equation Outperforms CG in Kidney Transplant Recipients

MDRD

Cockcroft-Gault

Poggio ED...Issa N et al, AJT 2006
Factors Affecting SCr (eGFR) in SOT

- **Decrease in muscle mass:**
  - Previous state of end organ failure (ESLD, Heart Failure..)
  - Highly catabolic states, i.e., steroid use, hospitalizations, meds, chronic diarrhea, other causes of weight loss, etc.

- **Hemodynamic renal changes:**
  - Volume depletion, edema, heart/liver failure, over-diuresis
  - Use of CNI, calcium channel blockers, ACEi/ARBs, NSAIDs, trimethoprim, etc.
Estimating Kidney Function in Clinical Transplantation

- Remember!!! **MDRD equation** Currently in use (and **CKD-EPI**) were derived from **non-transplant** subjects with CKD

- **Not applicable** to living kidney donors, non-renal transplant candidates with normal range SCr values, acute sickness or significant deconditioning

- **eGFR**: Acceptable to be used in the setting of **established Chronic Kidney Disease** pre- or post-transplant

- Always interpret estimated GFR and/or creatinine in the setting of H&PE & urinanalysis (proteinuria)

Poggio et al, Transplantation 2007; Issa et al, Transplantation 2008
Kidney Disease in SOT
Cumulative Risk of CKD Stages 4-5 (GFR <29 ml/min/1.73m²) Following SOT (n=69,321)

## Risk Factors for CKD in Solid Organ Transplant (SOT) Recipients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10-year increment)</td>
<td>1.36 (1.34 – 1.38)</td>
</tr>
<tr>
<td>Pre-tx GFR &gt;90</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>60-89 (CKD stage 2)</td>
<td>1.38 (1.30 – 1.46)</td>
</tr>
<tr>
<td>30-59 (CKD stage 3)</td>
<td>2.25 (2.12 – 2.39)</td>
</tr>
<tr>
<td>&lt;29 (CKD stage 4 – 5)</td>
<td>3.41 (3.15 – 3.70)</td>
</tr>
<tr>
<td>Post-operative renal failure</td>
<td>2.13 (1.99 – 2.27)</td>
</tr>
<tr>
<td>Pre-Tx dialysis</td>
<td>1.46 (1.27 – 1.68)</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.74 (0.71 – 0.77)</td>
</tr>
<tr>
<td>Tacrolimus use</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>CSA</td>
<td>1.24 (1.17 – 1.30)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>1.15 (1.08 – 1.23)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1.42 (1.33 – 1.51)</td>
</tr>
<tr>
<td>HTN</td>
<td>1.18 (1.10 – 1.26)</td>
</tr>
</tbody>
</table>

Patients with Previous Non-Renal Tx are a Rapidly Increasing Population **Preemptively** Listed for DD Kidney Tx

![Graph showing the increase in new solitary kidney transplant candidate listings for different organs from 1995 to 2008.](image)

<table>
<thead>
<tr>
<th>Candidate Population</th>
<th>% increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Adults</td>
<td>74%</td>
</tr>
<tr>
<td>Adults with Prior Kidney Tx</td>
<td>70%</td>
</tr>
<tr>
<td>Adults with Prior Liver Tx</td>
<td>330%</td>
</tr>
<tr>
<td>Adults with Prior Heart Tx</td>
<td>307%</td>
</tr>
<tr>
<td>Adults with Prior Lung Tx</td>
<td>635%</td>
</tr>
</tbody>
</table>

Srinivas T, CJASN Sep 2010
Patients with Previous SOT Died at a More Accelerated Rate Than Those Without Transplant

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Median Survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior transplant</td>
<td>7.5</td>
</tr>
<tr>
<td>Prior kidney transplant</td>
<td>9.2</td>
</tr>
<tr>
<td>Prior liver transplant</td>
<td>4.0</td>
</tr>
<tr>
<td>Prior heart transplant</td>
<td>3.8</td>
</tr>
<tr>
<td>Prior lung transplant</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Srinivas T, CJASN Sep 2010
UNOS Data Analysis of Incidence *Kidney Tx* after SOT

Lonze BE, AJT 2009
So Why Kidney Failure Post-SOT???
Relationship between AKI & CKD in SOT

A. General population
- No known CKD ➔ Triggering insult ➔ Acute kidney injury ➔ Recovery

B. Non-renal organ recipient population
- Pre-existing CKD (DM, HTN, HCV) ➔ Older Age ➔ Pre-txp insults
  - INFECTION
  - DRUG TOXICITY
  - RENAL HYPOPERFUSION
    - HRS
    - HYPOVOLEMIA
    - LOW CO
    - END-STAGE ORGAN FAILURE

- Acute kidney injury ➔ Incomplete recovery (ongoing insults)
  - TXP SURGERY
  - CNIs
  - SIROLIMUS
  - TXP ORGAN DYSFUNCTION

Bloom RD, JASN 2007
Organ-Specific Risk Factors

+ CNI + other

Kidney Disease
Timing of Kidney Injury

Pre-Tx Period

Heart and Liver > Lung/Pancreas/Gut

Organ-specific

Organ Tx

Peri-Tx and Immediate Post-Op Period

Acute decompensated end-stage organ disease + post-surgical morbidity

CNI exposure and other medical complications

Post-Tx and Long-term Period

All organs

High risk patients requiring high levels of CNI or other nephrotoxic drugs
Pre-transplant Risk Factors for Renal Dysfunction

- Renal hemodynamic perturbation
  - End-stage organ failure with effective volume contraction
    - Over-diuresis, hepatorenal syndrome, decompensated heart failure
- Acute kidney injury
  - IV Contrast, sepsis, hypotension, nephrotoxic drugs, etc.
- Prior history of conditions causative of CKD
  - DM, hypertension, hepatitis C or B, etc...
- Prior history of established CKD
  - Baseline pre-transplant GFR
  - Proteinuric vs. non-proteinuric disease
  - Period of time with the abnormal GFR
**Peri-transplant Risk Factors for Renal Dysfunction**

- Renal hemodynamic perturbation
  - Hypotension and renal hypoperfusion during or post surgery
  - Aortic cross-clamp and cardiac pump for heart/lung transplantation
  - Acute exposure to CNI in the immediate post-op period
- Immediate non-renal transplant dysfunction
- Perioperative ATN
- Infectious complications: sepsis…
- Prolonged hospital, ICU stays
**Post-transplant Risk** Factors for Renal Dysfunction

- Demographic variables (older age & female gender)
- Length of graft survival $\rightarrow$ prolonged CNI exposure
- **Intensity of the CNI exposure**
- Type of CNI use (cyclosporine vs. tacrolimus)
- Post-transplant DM, HTN, dyslipidemia
- Post-transplant microangiopathic anemia
Heart & Lung Transplantation
Renal Dysfunction in Heart and Lung Transplantation

- Very common
- Systemic atherosclerosis with likely microvascular renal disease
- Renal hypoperfusion due to Systolic HF
- Need for cardiopulmonary bypass during transplantation
- Immunogenic organs → higher trough levels of CNI
- Difficult to assess pre-tx state of kidney function
Acute Kidney Injury (AKI) after Heart Transplantation

- Retrospective analysis of 756 heart transplants recipients at the Cleveland Clinic
- 44 patients (5.8%) developed AKI requiring dialysis post transplant
- Pre-op risk factors for AKI development:
  - Pre-op CKD, DM, age and cardiopulmonary bypass time

Boyle J. et al. AJKD 2006
AKI after Heart Transplantation

- Retrospective analysis of 628 heart transplants recipients at UCLA
- Two groups of pts: Pre-TX eGFR > or < 40 ml/min (by Cockcroft-Gault)
  - **Higher mortality** in group with lower renal function (17% vs. 7%)
- AKI requiring HD: 9% vs. 32%
- Mortality post AKI: 3% vs. 41%

Odim et al., J of Heart and Lung Transplant 2006
AKI after Lung Transplantation

- Retrospective analysis of 296 lung transplant recipients (Duke)
- AKI defined as doubling of SCr within 2 weeks post-tx
- 3 groups: no AKI (n=130), AKI/no dialysis (n=143) and AKI/dialysis (n=23)
- Pre-op risk factors for AKI development:
  - Baseline GFR, use of nephrotoxic drugs like amphotericin B & aminoglycosides, & need for mechanical ventilation of greater than 1 day post transplant

Rocha et al., AJT 2005
Biphasic Decline of Kidney Function after Heart and Lung Transplantation

- 219 pts., 33 heart-lung, 66 double lungs and 120 single lung tx (U of M)
- Pre-tx GFR: 92 ml/min
- Doubling of SCr was 34%, 43% and 53% at 1, 2 and 5 years respectively / 7.3% developed ESRD
- Loss of renal function between the 2 groups occurred in the first 6 months

Ishani et al., KI 2002
Chronic Kidney Disease (CKD) after Lung and Heart Transplantation

- 219 lung and heart-lung transplant recipients (U of M)
- Pre-tx GFR: 96 ml/min/1.73 m²
- Doubling of SCr was 55% and 7% reached ESRD
- Factors associated with doubling of SCr: pre-tx and 1-month SCr, older age and use of CSA

Most of the GFR loss occurs during the first year post-tx

Canales et al. AJT 2006
CKD after Heart Transplantation

• Very common: up to 25% incidence

• About 5% of living heart tx recipients were on dialysis and ~1% had received a kidney tx (2005 ISHLT report)

• Worse outcomes compared to heart tx patients without CKD

• Initial rapid decline of GFR (first 6 months to 1 year) with later stabilization but decreased GFR

• Recipient age, pre-transplantation GFR, history of DM, and HTN are all associated with higher risk of developing CKD

CKD after Lung Transplantation

• Very common: ~30% incidence of CKD stage 4-5 at 5 years, >50% developed CKD stage 3 by 1 year; ~7% developed ESRD

• LAS: Sr Creatinine

• Initial rapid decline of GFR (first 6 months to 1 year) with later stabilization but decreased GFR

• CNI use plays a significant role in kidney disease

• Recipient age, pre & 1-month post-transplantation GFR, dyslipidemia, DM, and HTN are all associated with higher risk of developing CKD
Renal Dysfunction and Kidney Disease in Liver Transplantation

• Very common problem in the pre- and post-transplant
• Renal dysfunction is **NOT limited** to only renal hemodynamic compromise like HRS- high prevalence of HCV, subclinical glomerulonephritis is common
  - GN: IgA nephropathy, hepatitis B related GN, cryos, etc.
• Very dynamic changes in GFR, especially pre-tx period
• MELD score (Sr creatinine/RRT = sicker patient)
• Differentiation of reversible vs. non-reversible disease
• Assessment of chronicity/reversibility of renal dysfunction: Decision for SLK
• Pre-tx renal function negatively impacts post-tx outcomes
CKD after Liver Transplantation

CKD prevalence in 230 liver transplant recipients with 6 years of follow up

Female gender, age, pre-OLT proteinuria, lower GFR from 1 year and higher creatinine from 6 mos were associated with progression of CKD

GFR <30 ml/min associated with reduced patient survival

O’Riordan et al, NDT 2006
Renal Dysfunction after Pancreas or Allo-Islet Cell Transplantation

- Scarcity of data
- Benefits of achieving euglycemia vs. CNI nephrotoxicity take very long follow-up to study
- Decline in kidney function in the first 5 years → stable thereafter
- Worsening renal function and increased albuminuria in islet cell transplant recipient during first year post transplant

So Are the CNIs the Only Culprits??

WANTED

Cyclosporine or Tacrolimus!!

REWARD
Cyclosporine-Associated Chronic Nephropathy

BD Myers, J Ross, L Newton, J Luetscher, and M Perlroth

NEJM 1984

17 OHTx recipients on CSA vs. 15 OHTx recipients on AZA

GFR Decreased & More ESRD in the CSA Group

*Levels very high in the range of 300-350 ng/ml*
Mechanisms of *Acute* CNI Nephrotoxicity

- **Functional** pre-renal hemodynamic effects with minimal initial histological changes

- Vasospasm of glomerular afferent and efferent arterioles → acute reduction in GFR

- **Reversible**, drug-concentration dependent

- Similar effects of cyclosporine A and tacrolimus in the acute setting
Putative Mechanisms of **Chronic CNI Nephrotoxicity**

- Chronic vasoconstriction of renal microcirculation → chronic ischemia in addition to other insults on native kidneys
- Some studies showed correlation between CNI doses or blood concentrations and degree of chronic renal dysfunction
- **?? CNI Pathology:**
  - Atrophy and fibrosis of the tubulo-interstitium: Non-Specific
  - Severe hyalinization of arterioles: ? Specific/Non-Specific
  - Glomerulosclerosis and arteriosclerosis: Non-Specific
Is There A Specific Histology For Chronic CNI Nephrotoxicity??

- Striped fibrosis
- Hyalinosis
- Striped fibrosis
- Glomerular hypoperfusion
- Striped fibrosis
- Sclerosed glomerulus
There Are No Specific Histological Lesions For Chronic CNIs Nephrotoxicity In Kidney Transplants!

- Snanoudj et al. compared 48 kidney Tx recipients who received CSA vs. 93 who did not
- All patients underwent protocol biopsies at 3 mos, 2 & 10 yrs
- Arteriolar hyalinosis was more frequent & more severe in the CNIs group (92% of patients at 10 years) but also present in 65% of patients who were never exposed to CNIs

So Are Native Kidneys More Prone to CNI’s Nephrotoxicity Than Kidney Transplants?

CNI Nephrotoxicity:

- Increase in vasoconstrictor factors: endothelin, thromboxane, & activation of the RAS system
- Reduction of vasodilator factors: prostacyclin, prostaglandin, Nitric Oxide
- Free radicals formation
- *Sympathetic nerve activation in native kidneys* has been implicated in the pathogenesis of toxic effects of CNI
- Recipients of renal transplants lack the sympathetic innervation of the allograft—this innervation plays a prominent role in the regulation of renal vascular resistance
- CNI’s level targets are higher in (Heart, Lung, Pancreas) Tx
In Native Kidneys:

CNI’s up-regulates the RAAS / Innervation plays a prominent role in the regulation of renal vascular resistance via the sympathetic tone → renal vasoconstriction

The Answer: Native Kidneys Are Likely More Prone to CNI’s Nephrotoxicity Than Kidney Transplants
<table>
<thead>
<tr>
<th>Risk Factors for Calcineurin Inhibitor Nephrotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic overexposure to cyclosporine and tacrolimus</strong></td>
</tr>
<tr>
<td><strong>Local exposure to cyclosporine and tacrolimus interactions with drugs interfering with ABCB1-mediated transport in the tubular epithelial cells (e.g., mTOR inhibitors)</strong></td>
</tr>
<tr>
<td><strong>ABCB1 genotype of the kidney</strong></td>
</tr>
<tr>
<td><strong>ABCB1 expression in renal tubular epithelial cells</strong></td>
</tr>
<tr>
<td><strong>Exposure to metabolites of cyclosporine and tacrolimus</strong></td>
</tr>
<tr>
<td><strong>CYP3A4/5 genotype of the patient</strong></td>
</tr>
<tr>
<td><strong>CYP3A5 expression in renal tubular epithelial cells</strong></td>
</tr>
<tr>
<td><strong>interactions with other drugs which lead to altered exposure to calcineurin inhibitor metabolites (e.g. ketoconazole)</strong></td>
</tr>
<tr>
<td><strong>Older kidney age</strong></td>
</tr>
<tr>
<td><strong>Use of nonsteroidal anti-inflammatory drugs</strong></td>
</tr>
<tr>
<td><strong>Salt depletion and diuretic use</strong></td>
</tr>
<tr>
<td><strong>Genetic polymorphisms of other genes (e.g., TGF-β, ACE)</strong></td>
</tr>
</tbody>
</table>

**ABCB1**, ATP-binding cassette subfamily B, member 1; **TGF-β**, transforming growth factor β; **ACE**, angiotensin converting enzyme.
Chronic Use of CNI’s in SOT & Kidney Dysfunction: Is It As Simple As That?

WANTED

Cyclosporine or Tacrolimus !!

REWARD
The Variable Pathology of Kidney Disease Post-Liver Transplantation: Not All CNI’s!

• 81 OLT with creat > 1.5 mg/dL or new proteinuria; Mean time to biopsy = 4.8 yrs; Hep C

• All patients underwent kidney biopsy

• All biopsies demonstrated glomerular abnormalities, 42% showed primary glomerular diseases, & **only 15% had evidence of calcineurin inhibitor toxicity**

• “There is little CNI’s toxicity”

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**TABLE 2.** Histopathologic findings on kidney biopsy

<table>
<thead>
<tr>
<th>Light microscopy findings (n=81)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerular abnormalities</td>
<td>81 (100)</td>
</tr>
<tr>
<td>Glomerulosclerosis</td>
<td>40 (50)</td>
</tr>
<tr>
<td>Mild (&lt;20%)</td>
<td></td>
</tr>
<tr>
<td>Moderate (20%-40%)</td>
<td>33 (40)</td>
</tr>
<tr>
<td>Severe (&gt;40%)</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Increased mesangial matrix</td>
<td>65 (80)</td>
</tr>
<tr>
<td>Increased glomerular basement membrane thickness</td>
<td>39 (48)</td>
</tr>
<tr>
<td>Glomerular nodular expansion</td>
<td>23 (28)</td>
</tr>
<tr>
<td>Specific glomerular lesions</td>
<td>35 (43)</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>21 (26)</td>
</tr>
<tr>
<td>Membranous glomerulonephritis</td>
<td>9 (11)</td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Arterial abnormalities</td>
<td>81 (100)</td>
</tr>
<tr>
<td>Arteriomegaly</td>
<td>81 (100)</td>
</tr>
<tr>
<td>Mild arteriomegaly</td>
<td>61 (75)</td>
</tr>
<tr>
<td>Moderate arteriomegaly</td>
<td>20 (25)</td>
</tr>
<tr>
<td>Nodular hyalinosis (suggesting CNI toxicity)</td>
<td>13 (15)</td>
</tr>
<tr>
<td>Tubulointerstitial abnormalities</td>
<td>53 (65)</td>
</tr>
<tr>
<td>Interstitial fibrosis</td>
<td>53 (65)</td>
</tr>
<tr>
<td>Tubular atrophy</td>
<td>45 (55)</td>
</tr>
<tr>
<td>Increased tubular membrane thickness</td>
<td>22 (27)</td>
</tr>
</tbody>
</table>

**Electron microscopy findings of the glomeruli (n=74)**

| Podocyte effacement              | 65 (88)  |
| Increase GBM thickness           | 48 (65)  |
| GBM sub-endothelial widening     | 52 (70)  |
| GBM wrinkling                    | 34 (46)  |
| GBM deposits (intramembranous)   | 12 (16)  |
| Increase mesangial matrix        | 49 (62)  |
| Osmophilic granules              | 30 (40)  |
| Mesangial deposits               | 32 (43)  |

Kim J, Transplantation 2010 Jan 27;89(2):215-21
Renal Survival in Patients Who Had CNIs Withdrawn Was Comparable to Those who had CNIs Continued (P = ns)

Kubal C, Transplantation 2012
CKD after Heart Transplantation: No Benefit of Early Low CSA Target Levels!

- In 2000, target CsA levels were reduced in the 1st year
- The risk factors for the development of eGFR < 45 by 3 yrs: post-operative RRT, pre-Tx DM, older recipient age, female recipient but not CsA regimen
- Lower CSA levels were associated with less renal dysfunction at Year 1 (P = 0.008), there was no significant effect by Year 3 (P = 0.7)
- “The incidence of CKD increased with time and was not influenced by the CsA regimen”

Table 5. (a) Univariable analysis of risk factors for chronic kidney disease stage 3B or worse at 3 years and (b) multivariable logistic regression model for the development of chronic kidney disease stage 3B or worse at 3 years

Panel a

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-operative renal replacement therapy</td>
<td>4.95</td>
<td>0.002</td>
</tr>
<tr>
<td>Pretransplant MDRD eGFR per ml/min/1.73 m²</td>
<td>0.98</td>
<td>0.001</td>
</tr>
<tr>
<td>Pretransplant diabetes mellitus</td>
<td>4.59</td>
<td>0.002</td>
</tr>
<tr>
<td>Female recipient</td>
<td>1.78</td>
<td>0.088</td>
</tr>
<tr>
<td>Recipient age per year</td>
<td>1.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female cardiac donor</td>
<td>1.65</td>
<td>0.066</td>
</tr>
</tbody>
</table>

Panel b

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-operative renal replacement therapy</td>
<td>7.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pretransplant diabetes mellitus</td>
<td>4.23</td>
<td>0.005</td>
</tr>
<tr>
<td>Recipient age per year</td>
<td>1.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recipient female</td>
<td>2.30</td>
<td>0.029</td>
</tr>
<tr>
<td>Female cardiac donor</td>
<td>1.86</td>
<td>0.043</td>
</tr>
</tbody>
</table>

Hamour M., Nephrol Dial Transplant. 2009
AKI Post-Lung Tx Increases The Risk of CKD

Figure 3  Repeated model of linear measure of estimated glomerular filtration rate at different interval and stratified by acute kidney injury (AKI) stages according to the Acute Kidney Injury Network (AKIN) classification. AKIN 2–3 vs no AKI, $p = 0.019$; AKIN 1 vs no AKI, $p = 0.085$; AKIN 2–3 vs AKIN 1, $p = 0.14$. 

Wehbe E, J Heart Lung Transplant. 2012 Mar;31(3):244-51
AKI Post-Lung Tx Increases The Risk of All Cause-Mortality

Figure 4  Survival curves after lung transplants by the different stages of acute kidney injury (AKI) are shown by Acute Kidney Injury Network (AKIN) classification. AKIN 1 vs no AKI, log-rank $p = 0.001$; AKIN 2–3 vs no AKI, log-rank $p < 0.001$; AKIN 2–3 vs AKIN 1, log-rank $p = 0.04$. 

Wehbe E, J Heart Lung Transplant. 2012 Mar;31(3):244-51
AKI (Regardless of the etiology) Is Associated With Long-Term Mortality

• AKI is associated with long-term adverse outcomes and is not solely limited to those with the most severe forms of AKI requiring dialysis

• *Recent meta-analysis showed that all severities of AKI, even the mildest forms are associated, with long-term mortality—“insignificant” AKI (i.e. a change in creatinine of only 0.3 mg/dl)

• Elderly Medicare beneficiaries who were discharged alive after an acute MI- those with AKI had a 10% to 39% increased risk for death during a 10-year period compared with patients without AKI

Evaluation of Kidney Dysfunction after SOT

• Physical and history focusing on risk factors for CKD (i.e., DM, HTN, hyperlipidemia, duration of CNI exposure)
• Estimate baseline pre-Tx and current kidney function
• Estimate progression of kidney disease over time
• Assess kidney size (renal U/S); biopsy when appropriate
• UA, assess presence and degree of proteinuria
• Comorbidities associated with CKD: anemia, bone disease, HTN, etc
Management of Kidney Disease in SOT

• No data from prospective trials regarding ideal approach
• Minimization of CNI’s when possible
• Treatment of associated medical conditions
  – DM
  – HTN
  – Anemia
  – Dyslipidemia
• Proper assessment of GFR pre-transplantation
• Regular screening for proteinuria/ Use of ACEi/ARBs in proteinuric CKD
• CKD **may be inevitable** until preventive measures for AKI are found and safe and efficacious non-nephrotoxic IS is introduced into clinical transplantation
Kidney Transplantation Confers Better Survival to SOT Recipients

Figure 2. Relative Risk of Death Associated with the Method of Renal Replacement (Dialysis or Kidney Transplantation) among Recipients of Nonrenal Organ Transplants Who Had Chronic Renal Failure.

Patient Survival is Better Among Prior Heart Recipients After Renal Tx vs. Remaining on the Waiting List

Lonze BE, AJT 2009
Patient Survival is Better Among Prior Lung Tx after Renal Transplantation vs. Remaining on the Waiting List

Lonze BE, AJT 2009
Summary & Conclusions

• Kidney disease, either acute or chronic is very common following non-renal solid organ transplantation.

• Despite its limitations, estimated GFR (MDRD) is a better tool to assess kidney function than SCr alone.

• Kidney disease is associated with worse transplant outcomes.

• CNI exposure (which remains the mainstay of contemporary immunosuppressive regimens), plays a major role but does not seem to be the sole kidney insult! Perhaps injury from CNIs is an early phenomenon, which is potentiated by surgery.

• Early detection and treatment of co-morbidities are important to delay progression of CKD.

• Some risk factors are not modifiable but measures to reduce the incidence of post-operative AKI may help to reduce CKD / ? Reno-protective strategies.
Multiple Factors Contribute to the Development of CKD Following Non-Renal Organ Transplantation: complex process and cannot be explained by calcineurin injury alone!!

<table>
<thead>
<tr>
<th>ATN/Peri-operative renal failure</th>
<th>Sepsis</th>
<th>Diuretics use</th>
<th>Exposure to IV contrast agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atheroembolism</td>
<td>Acute interstitial nephritis</td>
<td>Anemia</td>
<td>Ventricular Dysfunction</td>
</tr>
<tr>
<td>Increasing recipient/donor age</td>
<td>Diabetes Mellitus</td>
<td>Hypertension</td>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>Hepatitis B or C infections</td>
<td>Administration of nephrotoxic drugs: CNI</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Summary and Conclusions

• In view of the high incidence of CKD and the excess risk of death associated with it, it seems prudent to counsel patients undergoing transplantation of a nonrenal organ about the likelihood of CKD, just as they are typically cautioned about the risks of other complications — such as post-transplantation cancer, which occurs much less frequently than chronic renal failure!

• Treatment of ESRD with kidney transplantation in the non-renal organ transplant population has been associated with a nearly 50% reduction in mortality compared to other renal replacement therapy options / Fairness of Deceased Donor Kidneys allocation
Thank You!!!