Dr. Jeffrey Schiff is an Assistant Professor of Medicine at the University of Toronto. He trained in kidney and kidney-pancreas transplantation at McGill University and l’Université de Montréal. He subsequently joined the Division of Nephrology and the Multi-Organ Transplant Program at University Health Network, where he is a member of the Kidney Transplant Program and the Medical Director of the Pancreas Transplant Program. His clinical focus is on kidney and kidney-pancreas transplantation. He also developed the Renal Transplant Young Adult Transfer Clinic, in order to improve the transition of renal transplant recipients from pediatric to adult care. Dr. Schiff is active in transplant education at the local and national level. He is currently the Deputy Program Director of the Adult Nephrology Training Program at the University of Toronto, and Program Director of the Renal Transplant Fellowship, which is one of the largest kidney transplant fellowship programs in North America. He is also active in education through the Canadian Society of Transplantation, where he is Chair of the Education Committee. He has developed free web-based tools for transplant education, including Transplant Pearls and Transplant Now. He is also a member or chair of a variety of committees through Canadian Blood Services to help it in its role in improving organ donation and transplantation across Canada.
Disclosure

Jeffrey Schiff, MD

Grant/Research Support:

Consultant/Speaker Fees:
Kidney Disease in Non-Renal Transplant Recipients

Jeffrey Schiff, MD, FRCP(C)
Medical Director, Pancreas Transplant Program
Division of Nephrology and Multi-Organ Transplant Program,
University Health Network
Objectives

- Describe the incidence of kidney disease (CKD) post-transplant
- Review common causes of kidney disease in non-renal solid organ transplant patients
- Analyze results of randomized controlled trials of immunosuppression changes to preserve renal function
- Discuss the role of renal transplant in non-renal transplant patients with ESRD
Case Presentation

- 60-year-old woman
- Double lung transplant 5 years ago for emphysema
  - Excellent lung function
- Hypertension x 1 year
- Osteoporosis
- 45 pack-year smoking history, quit x 13 years
- No history of diabetes, dyslipidemia, CAD, CVA, PVD
Case Presentation

- Current medications
  - Cyclosporine, Myfortic, prednisone
  - Amlodipine 5 mg daily
  - Septra, azithromycin, calcium carbonate, vitamin D, omeprazole, domperidone, folic acid, paroxetine, bupropion, clonazepam

- No history of renal disease pre-transplant
- No urologic, renal or uremic symptoms
- No history of acute kidney injury, dialysis
Case Presentation

- **O/E**
  - BMI 29.1
  - BP 140/84
  - Remainder of exam unremarkable

- **Labs**
  - Hb 123 g/L
  - Normal electrolytes, Ca/PO4/albumin
  - Creatinine 120 µmol/L (eGFR 40 ml/min), 129-175 over last 4 years
  - 24-hr urine creatinine clearance 72 ml/min pre-transplant
  - Urinalysis negative for blood and protein
Case Presentation

- What is this woman’s underlying diagnosis?
- Does she need a renal biopsy?
- Should her immunosuppression be changed in order to preserve renal function?
- What else can be done to preserve her renal function?
Renal Function Is Often Abnormal and Misestimated Pre-Transplant

- Serum creatinine often normal in patients with end-stage organ disease
  - Decreased creatinine production in cirrhosis
  - Decreased muscle mass due to malnutrition
- Effects of end-organ disease or treatments may affect renal function or renal blood flow
  - Hypotension in advanced heart failure
  - Hepatorenal syndrome
  - Diuretics, ACE-inhibitors, ARBs
  - Nephrotoxic antibiotics
- Cockroft-Gault, MDRD and CKD-EPI equations may be inaccurate
- 24-hour urine collection may not be any better
Acute Kidney Injury- Common, Deadly, and Leads to CKD

- Retrospective study of 359 liver transplants in 300 patients
- Identified patients with acute renal injury (2x increase in creatinine) and acute renal failure (3x increase or dialysis)
- ARI (11.1%) and ARF (25.7%) were common post-transplant

<table>
<thead>
<tr>
<th>Table 5: Cox regression multivariate analysis of the effect of risk factors on 30-day and 1-year patient survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day patient survival</td>
</tr>
<tr>
<td>Fulminant hepatic failure</td>
</tr>
<tr>
<td>Inotrope use</td>
</tr>
<tr>
<td>Rejection</td>
</tr>
<tr>
<td>Hemorrhage</td>
</tr>
<tr>
<td>ARF</td>
</tr>
</tbody>
</table>

| 1-year patient survival                                     | p  | HR  | 95% CI     |
|---------------------------------------------------------------|
| Diabetes mellitus                                            | 0.02| 1.9 | 1.1–3.3    |
| Pre-OLT creatinine                                           | 0.19|     |            |
| Primary biliary cirrhosis                                    | 0.41|     |            |
| Inotrope use                                                | 0.17|     |            |
| Cytomegalovirus infection / disease                         | 0.03| 4.9 | 1.1–19.3   |
| Rejection                                                   | 0.69|     |            |
| ARF                                                         | 0.001| 2.6 | 1.5–4.5    |

ARF: acute renal failure; OLT: orthotopic liver transplantation; HR: hazard ratio; CI: confidence interval.
CKD is Common Post-Transplant

Stage 4 and 5 CKD only

## Table 3. Risk Factors Associated with Chronic Renal Failure in Recipients of Nonrenal Organ Transplants.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall Relative Risk (95% CI)</th>
<th>P Value</th>
<th>Relative Risks in Subgroups of Recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Liver Transplants</td>
</tr>
<tr>
<td>Age (per 10-year increment)</td>
<td>1.36 (1.34–1.38)</td>
<td>&lt;0.001</td>
<td>1.29</td>
</tr>
<tr>
<td>Pretransplantation glomerular filtration rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \geq 90 \text{ ml/min/1.73 m}^2 )</td>
<td>1.00 (reference group)</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>( 60–89 \text{ ml/min/1.73 m}^2 )</td>
<td>1.33 (1.30–1.46)</td>
<td>&lt;0.001</td>
<td>1.54</td>
</tr>
<tr>
<td>( 30–59 \text{ ml/min/1.73 m}^2 )</td>
<td>2.25 (2.12–2.39)</td>
<td>&lt;0.001</td>
<td>2.54</td>
</tr>
<tr>
<td>( \leq 29 \text{ ml/min/1.73 m}^2 )</td>
<td>3.41 (3.15–3.70)</td>
<td>&lt;0.001</td>
<td>3.78</td>
</tr>
<tr>
<td>Missing or unknown</td>
<td>1.33 (1.21–1.46)</td>
<td>&lt;0.001</td>
<td>1.25</td>
</tr>
<tr>
<td>Postoperative acute renal failure:‡</td>
<td>2.13 (1.99–2.27)</td>
<td>&lt;0.001</td>
<td>2.11</td>
</tr>
<tr>
<td>Dialysis treatment before transplantation</td>
<td>1.46 (1.27–1.68)</td>
<td>&lt;0.001</td>
<td>1.43</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.74 (0.71–0.77)</td>
<td>&lt;0.001</td>
<td>0.71</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.00 (reference group)</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Black</td>
<td>1.02 (0.95–1.10)</td>
<td>0.57</td>
<td>1.01( t )</td>
</tr>
<tr>
<td>Asian</td>
<td>0.77 (0.66–0.89)</td>
<td>&lt;0.001</td>
<td>0.79</td>
</tr>
<tr>
<td>Other</td>
<td>0.73 (0.63–0.85)</td>
<td>&lt;0.001</td>
<td>0.76</td>
</tr>
<tr>
<td>Calcineurin-inhibitor treatment during initial hospitalization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>1.00 (reference group)</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Calcineurin</td>
<td>1.24 (1.17–1.30)</td>
<td>&lt;0.001</td>
<td>1.25</td>
</tr>
<tr>
<td>Sirolimus treatment during initial hospitalization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00 (reference group)</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>1.19 (0.94–1.52)</td>
<td>0.16</td>
<td>1.21( \dagger )</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1.06 (0.96–1.18)</td>
<td>0.25</td>
<td>1.04( \dagger )</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>1.15 (1.08–1.23)</td>
<td>&lt;0.001</td>
<td>1.22</td>
</tr>
<tr>
<td>Hypertension before transplantation</td>
<td>1.13 (1.10–1.26)</td>
<td>&lt;0.001</td>
<td>1.04( \dagger )</td>
</tr>
<tr>
<td>Diabetes mellitus before transplantation</td>
<td>1.42 (1.33–1.51)</td>
<td>&lt;0.001</td>
<td>1.39</td>
</tr>
<tr>
<td>Year of transplantation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1998–2000</td>
<td>1.00 (reference group)</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>1994–1997</td>
<td>1.08 (1.02–1.14)</td>
<td>0.008</td>
<td>1.23</td>
</tr>
<tr>
<td>1990–1993</td>
<td>1.31 (1.15–1.48)</td>
<td>&lt;0.001</td>
<td>1.52</td>
</tr>
</tbody>
</table>

*Ojo et al NEJM 2003;349:931

\( t \) P  \leq 0.10

\( \dagger \) P  \leq 0.05

\( \S \) P  \leq 0.01

\( \dagger \) P  \leq 0.001
### Liver Program

<table>
<thead>
<tr>
<th>MDRD eGFR Range</th>
<th>Dialysis</th>
<th>Neph</th>
<th>Neph + Dialysis</th>
<th>Grand Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 15</td>
<td>5</td>
<td>1</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>15 - 29</td>
<td>22</td>
<td>29</td>
<td>1</td>
<td>52</td>
</tr>
<tr>
<td>30 - 59</td>
<td>399</td>
<td>3</td>
<td>112</td>
<td>2</td>
</tr>
<tr>
<td>60 - 89</td>
<td>547</td>
<td>2</td>
<td>28</td>
<td>577</td>
</tr>
<tr>
<td>&gt;= 90</td>
<td>209</td>
<td>2</td>
<td>211</td>
<td>211</td>
</tr>
<tr>
<td><strong>Grand Total</strong></td>
<td><strong>1182</strong></td>
<td><strong>6</strong></td>
<td><strong>187</strong></td>
<td><strong>6</strong></td>
</tr>
</tbody>
</table>

### Lung Program

<table>
<thead>
<tr>
<th>MDRD eGFR Range</th>
<th>Dialysis</th>
<th>Neph</th>
<th>Neph + Dialysis</th>
<th>Grand Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 15</td>
<td>5</td>
<td>11</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>15 - 29</td>
<td>43</td>
<td>41</td>
<td>2</td>
<td>86</td>
</tr>
<tr>
<td>30 - 59</td>
<td>282</td>
<td>4</td>
<td>91</td>
<td>379</td>
</tr>
<tr>
<td>60 - 89</td>
<td>155</td>
<td>1</td>
<td>14</td>
<td>170</td>
</tr>
<tr>
<td>&gt;= 90</td>
<td>60</td>
<td>2</td>
<td>2</td>
<td>62</td>
</tr>
<tr>
<td><strong>Grand Total</strong></td>
<td><strong>545</strong></td>
<td><strong>5</strong></td>
<td><strong>159</strong></td>
<td><strong>715</strong></td>
</tr>
</tbody>
</table>
Causes of Chronic Kidney Disease Post-Transplant

- Calcineurin inhibitor nephrotoxicity
- Previous acute kidney injury/acute tubular necrosis
- Pre- or post-transplant
  - Hypertension
  - Diabetes
- Atherosclerotic renal disease
- Primary or secondary glomerulonephritis
  - HBV- or HCV-related
  - De novo
- Rare: thrombotic microangiopathy, polyomavirus nephropathy
Nephrotoxicity of Calcineurin Inhibitors

- Acute reversible decrease in GFR
  - Afferent arteriolar vasoconstriction

- Chronic progressive or non-progressive decrease in GFR
  - Hypertension
  - Bland urinary sediment
  - Proteinuria uncommon
  - Interstitial fibrosis and tubular atrophy
  - Arteriolar hyalinosis

- Acute or chronic thrombotic microangiopathy - rare
Acute CnI Toxicity

English et al, Transplantation 1984;44:135
What Defines CnI Toxicity?

- Protocol biopsy study in RTx recipients
- Development of all chronic changes of CnI toxicity in patients, regardless of IS

Snanoudj et al, Am J Transpl 2011;11:2635
Chronic CnI Toxicity Post-Nonrenal Transplant

- Allows for “cleaner” assessment of CnI effect
  - Not confounded by rejection, ischemia-reperfusion injury, recurrent disease, etc.

- Most reports of histologic changes are biased
  - Single-center
  - For-cause biopsies
  - Most patients deviate from typical natural history
Common Histologic Findings

- **Non-specific**
  - Interstitial fibrosis and tubular atrophy
  - Arteriolar hyalinosis

- **Possibly specific**
  - Focal segmental glomerulosclerosis

- **Specific**
  - Diabetic nephropathy
  - Glomerulonephritis (e.g. MPGN, membranous nephropathy, IgA)
  - Thrombotic microangiopathy
  - Polyomavirus nephropathy
When to Biopsy?

- Active urinary sediment
- Proteinuria
- Rapid change in renal function
- Uncertainty about diagnosis
Immunosuppressive Strategies to Preserve Renal Function

- Delayed calcineurin inhibitor introduction
- Calcineurin inhibitor substitution
- Calcineurin inhibitor reduction
- Calcineurin inhibitor avoidance
Delayed CNI Introduction

- Open-label multi-center RCT
- Patients randomized to:
  - Tacrolimus, MMF, steroids
  - Daclizumab, tacrolimus delayed to day 5, MMF, steroids
- Target tacrolimus levels 10-20 ng/mL for first 4 weeks, then 5-15 ng/mL
- Primary endpoint percentage of patients with serum creatinine >130 µmol/L at 6 months post-transplant
- Primary endpoint reached in delayed tacrolimus group 22.4% vs. 29.7% in standard group (p=NS)

Calmus et al, Transplantation 2010;89:1504
CNI Substitution

- Replace calcineurin inhibitor with sirolimus or MPA

- Key issues:
  - Renal function at time of substitution
  - Timing of conversion
  - Medication side effects
  - Safety - rejection, graft loss
Liver Spare The Nephron (STN) : Study Design

**Inclusion**
Adult patients (18 to 74 yrs)
Randomization: 30-90 days post Tx

Treated with CNI + MMF + Steroids

1:1 Randomization (N = 293)

**SRL Conversion (n = 148)**
- MMF (1-1.5g BID)
- Sirolimus (2-4 mg/day; trough 5-10ng/ml)
- MEAN TIME =52 +/- 11 days

**CNI Continuation (n = 145)**
- Tac (0.1-0.15mg/day; trough 3-10ng/ml)
- CsA (3-5 mg/kg BID; trough 100-250 ng/ml)
- MEAN TIME = 50 +/- 10 days

Liver Spare the Nephron (STN): Change From Baseline in Glomerular Filtration Rate (GFR)

Change (Mean Percentage) From Baseline in GFR

- **6 month:** $P < 0.0001$
- **12 month:** $P = 0.0012$
- **24 month:** $P = 0.0053$

## Liver Spare the Nephron (STN): Safety Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>CNI + MMF</th>
<th>SRL + MMF</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPAR (up to 24 mo)</td>
<td>6 (4.1%)</td>
<td>18 (12.2%)</td>
<td>0.0159</td>
</tr>
<tr>
<td>Graft loss (up to 24 mo)</td>
<td>14 (9.7%)</td>
<td>8 (5.4%)</td>
<td>0.1175</td>
</tr>
<tr>
<td>Death</td>
<td>10</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Treatment failure (to 12 mo)</td>
<td>55 (37.9%)</td>
<td>72 (48.6%)</td>
<td>0.0845</td>
</tr>
<tr>
<td>Patients with at least 1 SAE</td>
<td>65 (45%)</td>
<td>67 (45%)</td>
<td>NS</td>
</tr>
<tr>
<td>Discontinuation due to AE or infection</td>
<td>37 (25%)</td>
<td>53 (36%)</td>
<td></td>
</tr>
<tr>
<td>New onset or worsening hyperlipidemia</td>
<td>50.0%</td>
<td>70.3%</td>
<td>0.0004</td>
</tr>
<tr>
<td>New onset or worsening diabetes mellitus</td>
<td>26.7%</td>
<td>14.2%</td>
<td>0.0084</td>
</tr>
<tr>
<td>New or worsening malignancy</td>
<td>10 (6.8%)</td>
<td>7 (4.7%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Wyeth Study 313: Study Design

**Inclusion**
6 months to 12 yrs after liver transplantation
CNI-based immunosuppression
Anti-metabolite therapy permitted

2:1 Randomization (N = 607)

SRL Conversion (n = 393)
SRL troughs: 8-16 ng/mL
± anti-metabolite (AZA or MMF)

CNI Continuation (n = 214)
Continue CNI (CsA: 50-250; TAC 3-10)
± anti-metabolite (AZA or MMF)

## Study 313 - Primary and Secondary Endpoints

### Baseline to 12 Months

<table>
<thead>
<tr>
<th></th>
<th>SRL Conversion</th>
<th>CNI Continuation</th>
<th>P- Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Participants</td>
<td>393</td>
<td>214</td>
<td></td>
</tr>
<tr>
<td><strong>PRIMARY ENDPOINT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from Baseline Adjusted Mean GFR (mL/min)</td>
<td>-4.45 ± 1.12</td>
<td>-3.07 ± 1.36</td>
<td>0.342</td>
</tr>
<tr>
<td><strong>SECONDARY ENDPOINTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graft Survival</td>
<td>367 (93.4%)</td>
<td>202 (94.4%)</td>
<td>0.356</td>
</tr>
<tr>
<td>Graft Loss</td>
<td>26</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>13 (3.3%)</td>
<td>3 (1.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Biopsy-Confirmed Acute Rejection</td>
<td>46 (11.7%)</td>
<td>13 (6.1%)</td>
<td>0.017</td>
</tr>
<tr>
<td>Serum Creatinine (µmol/L)</td>
<td>119.0 ± 38.9</td>
<td>122.4 ± 31.5</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>


Pfizer Study 408: Safety And Efficacy Of Conversion From CNI To SRL In Renally-Impaired Heart Transplant Recipients

Open-label, randomized, comparative, multicenter, multinational study

Adult cardiac transplant recipients; mild to moderate renal insufficiency (> 40, < 90 ml/min)
≥ 12mo, ≤ 96 mo after transplantation

1:1 Randomization (N = 116)

SRL Conversion (n = 57)
- SRL troughs: 7–15 ng/mL
- CNI discontinued by 8 weeks
- Continue MMF, MPS, or AZA
- Continue (±) corticosteroids

CNI Continuation (n = 59)
- Continue CsA (50-250 ng/mL) or TAC (3-10 ng/ml)
- Continue MMF, MPS, or AZA
- Continue (±) corticosteroids

AZA, azathioprine; CsA, cyclosporine A; MMF, mycophenolate mofetil; MPS, mycophenolate sodium

Study 408: Adjusted Mean Change (± SE) from Baseline in Estimated Creatinine Clearance

**Intent-To-Treat (LOCF)**

- **Week 24**: SRL 2.2 ± 1.4, CNI -1.9 ± 1.3
- **Week 52**: SRL 3.0 ± 1.3, CNI -1.4 ± 1.2

**On-Therapy**

- **Week 24**: SRL 6.3 ± 1.6, CNI -2.6 ± 1.3
- **Week 52**: SRL 4.7 ± 1.7, CNI -2.1 ± 1.7

*P = 0.012 for SRL vs CNI at Week 24, P = 0.004 at Week 52.*

*http://www.clinicaltrials.gov NCT00369382 Accessed Feb 2012*
### Study 408: Survival and Acute Rejection

<table>
<thead>
<tr>
<th></th>
<th>SRL (n=57)</th>
<th>CNI (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, n/N (%)</td>
<td>2/57 (3.5)</td>
<td>0/57 (0.0)</td>
</tr>
<tr>
<td>Biopsy-confirmed acute rejection, n/N (%)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol mandated</td>
<td>7/39 (18.0)</td>
<td>N/A</td>
</tr>
<tr>
<td>For cause†</td>
<td>5/57 (8.8)</td>
<td>1/57 (1.8)</td>
</tr>
<tr>
<td>Site protocol†</td>
<td>2/11 (18.2)</td>
<td>0/11 (0)</td>
</tr>
<tr>
<td>Acute rejection with hemodynamic compromise, n/N (%)†‡</td>
<td>1/57 (1.8)</td>
<td>1/57 (1.8)</td>
</tr>
</tbody>
</table>

*Biopsy grade 2R or higher (ISHLT 2005 criteria), rejection accompanied by hemodynamic compromise or requiring treatment
†Between-group comparison, P=NS.
‡Diagnosed on biopsies done for cause.

CnI Avoidance

- Use of sirolimus beginning at time of transplant
- One retrospective study showing similar outcomes of sirolimus alone compared to sirolimus with CnI and CnI alone
- No randomized controlled studies to confirm results
- Concerns of impaired wound healing, thrombocytopenia

Zaghla et al, Aliment Pharmacol Ther 2006;23:513
Non-Immunosuppressive Management of CKD

- Blood pressure control
  - Target 130/80
  - No data favouring any antihypertensive class
  - Exception: ACE-I or ARB in patients with proteinuria

- Glycemic control
  - Aggressive control in diabetic patients

- Dyslipidemia
  - Lipid targets as for patients with known CVD

- Prophylactic ASA
Non-Immunosuppressive Management of CKD

- Calcium/phosphate/PTH
  - Dietary control of phosphate
  - Calcium supplements with meals
  - Calcitriol

- Anemia
  - Iron supplementation
  - Erythropoietin/Darbepoietin

- Nutrition
  - Adequate protein intake

- Timely initiation of renal replacement therapy
Renal Transplantation in Liver Transplant Patients with ESRD

- Liver transplant patients do poorly on dialysis
- Already exposed to risks of immunosuppression
- Better outcomes overall with transplant than on dialysis
- Similar findings in heart transplantation

Al Riyami et al, Transplantation 2008;85:1277
Should Non-renal Transplant Patients with ESRD Be Prioritized for Transplant?

**Pro**

- Very high mortality risk on dialysis reversed by transplantation
- Would improve outcomes of non-renal transplants
- Is often due to iatrogenic cause, i.e. calcineurin inhibitors

**Con**

- No priority given for patients with other high-risk comorbidities (e.g. diabetes)
- Would disadvantage patients requiring a kidney transplant alone
- May result in selection of higher-risk patients for transplant
Summary

- A common and important problem post-transplant
- Affects long-term outcomes
- Most commonly, but not always, due to calcineurin inhibitor toxicity
- Other common diseases, such as diabetes and hypertension, also contribute
- More likely to see benefit of immunosuppressive changes when done early post-transplant
- Data on best non-immunosuppressive management lacking