KIDNEY TRANSPLANTATION
FOR THE INTERNIST

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South Florida Kidney Disease and Hypertension Specialists
BRRH Grand Rounds 5.8.2018
Goal of Lecture:
OUTLINE

- CKD -> ESRD
- Workup for Transplant
- UNOS Registry
- Immune Suppression
- Infectious Complications
- Noninfectious Complications
- Prognosis
**CKD STAGES**

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR Categories (mL/min/1.73 m²)</th>
<th>Description</th>
<th>Persistent Albuminuria Categories, Description and Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal or high</td>
<td>≥90</td>
<td>Normal to mildly increased 30 mg/g (&lt;3 mg/mmol) Moderate increased &gt;30 mg/g (&gt;3 mg/mmol)</td>
</tr>
<tr>
<td>2</td>
<td>Mildly decreased</td>
<td>60–89</td>
<td>1 if CKD 30-300 mg/g (3-30 mg/mmol) 3 if CKD &gt;300 mg/g (&gt;30 mg/mmol)</td>
</tr>
<tr>
<td>3a</td>
<td>Mildly to moderately decreased</td>
<td>45–59</td>
<td>1 if CKD 30-300 mg/g (3-30 mg/mmol) 3 if CKD &gt;300 mg/g (&gt;30 mg/mmol)</td>
</tr>
<tr>
<td>3b</td>
<td>Moderately to severely decreased</td>
<td>30–44</td>
<td>2 if CKD 30-300 mg/g (3-30 mg/mmol) 3 if CKD &gt;300 mg/g (&gt;30 mg/mmol)</td>
</tr>
<tr>
<td>4</td>
<td>Severely decreased</td>
<td>15–29</td>
<td>3 if CKD 30-300 mg/g (3-30 mg/mmol) 4 if CKD &gt;300 mg/g (&gt;30 mg/mmol)</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15</td>
<td>4 if CKD 30-300 mg/g (3-30 mg/mmol) 5 if CKD &gt;300 mg/g (&gt;30 mg/mmol)</td>
</tr>
</tbody>
</table>
Prevalence of ESRD is Rising

- Incidence leveling off but prevalence up
HD vs TRANSPLANT

Number of ESRD Patients by Treatment Modality

- Transplant Patients: 172,553
- Dialysis Patients: 398,861

Dialysis Patients:
- Other or uncertain dialysis: 1,262
- Continuous cycler-assisted peritoneal dialysis: 18,064
- Continuous ambulatory peritoneal dialysis: 9,458
- Home HD: 4,511
- In-center HD: 365,566

Graphs showing number of transplants over years:
- All transplants
- Deceased donor
- Living donor

Years: 04, 06, 08, 10, 12, 14

NIDDK
More eligible patients and plateauing living donor rates → higher WL times
Advertising???
How to increase # kidney txp?

- “Opt-out” vs “opt-in” policy
- Dispelling myths re: living donation
- Swaps/Chains
- Expanded Criteria Donor (ECD) List
  - > 60
  - >50 plus 2 of 3: HTN, CVA, Cr > 1.5
- Accepting kidneys from previously “marginal” living donors
- ABOi transplants
- HCV+ Donor
ESRD costs Medicare $29 billion per year!!!
Transplant Benefits: Mortality

Patient Survival Rates by Dialysis and Transplant

- **Dialysis Patients**
- **Transplant Patients**

<table>
<thead>
<tr>
<th>Year</th>
<th>Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>100</td>
</tr>
<tr>
<td>2 years</td>
<td>90</td>
</tr>
<tr>
<td>3 years</td>
<td>80</td>
</tr>
<tr>
<td>4 years</td>
<td>70</td>
</tr>
<tr>
<td>5 years</td>
<td>60</td>
</tr>
</tbody>
</table>

- *1 year (2008–2009)*
- *2 years (2007–2009)*
- *3 years (2006–2009)*
- *4 years (2005–2009)*: No data available
- *5 years (2004–2009)*
Transplant Benefits: Mortality

Mortality (% Per Year)
Dialysis vs. Transplant

- dx not listed
- dx listed
- txp
- dx failed txp
Less mortality and less rejection
More living transplant patients

- 200k
- Fastest growing > 50
- We need help caring for these patients!
Kidney Transplant Referral

- Eligible if irreversible progression to GFR < 20mL/min
Who can be referred?

- Just about anybody!

- **Absolute** contraindications:
  - Active malignancy
  - Active untreated infection
  - Severe irreversible extrarenal disease
  - Psychosocial issues

- Note what’s **not** on this list:
  - Age, HIV, HCV, patients eligible for dual organ transplant
Florida Organ Procurement Offices (OPO)

- Our local zone:
  - UM/Jackson
  - Cleveland Clinic- FL
  - Memorial Hollywood *new*

- Pts can be referred to multiple zones
Recipient Pre-txp Workup

- Basic Labs
- Drug screen
- Infection screen
- Age appropriate cancer screening
- HLA/ABO testing
- Cardiac testing based on RF
- Dental clearance
- Etc
Living Donation

- Medical, Surgical, and Psychosocial evaluation
- Purpose: protect the donor!

- Periop 90 day mortality - 1 in 3000 (0.03%)

- Long term:
  - No change in mortality compared to controls
  - Slightly increased relative risk of HTN, PEC, ESRD
    - (absolute risk low)
Kidney Transplant Surgery

- Iliac Fossa
- Anastomoses:
  - Renal A/V
  - Ureter
- Native kidneys remain!
Transplant Medications

Figure 2. Individual Immunosuppressive Drugs and Sites of Action in the Three-Signal Model.
Maintenance therapy

- **Calcineurin Inhibitors**
  - Tacrolimus > Cyclosporine
  - Inhibits transcription of IL2 and other cytokines → less T cell activation

- **Antiproliferatives**
  - Mycophenolate > Azathioprine
  - Interferes with DNA/purine synthesis

- **Steroids**
  - Prevents cytokine production by T cells and APCs

- **Also:** mTOR inhibitors, Belatacept
## Drug Toxicity

<table>
<thead>
<tr>
<th>Combination</th>
<th>Hypertension</th>
<th>Diabetes</th>
<th>Hyperlipidemia</th>
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<tbody>
<tr>
<td>Azathioprine</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Prednisone</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>++</td>
<td>+++++</td>
<td>++</td>
</tr>
<tr>
<td>MMF</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>0</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Everolimus</td>
<td>0</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Belatacept</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</table>
CNI Nephrotoxicity

- Glomerular afferent/efferent arteriolar vasoconstriction

**Light micrograph showing cyclosporine-induced arteriopathy**

Light micrograph of cyclosporine-induced renal arteriopathy. There is replacement of smooth muscle cells in the media by proteinaceous material (arrowheads), eventually leading to virtual obliteration of the vascular lumen (arrow).

**Light micrograph showing cyclosporine-induced renal tubular injury**

Light micrograph shows vacuolization of the proximal tubular cells (arrows) due to cyclosporine nephrotoxicity.
CNI Toxicity (cotd)

- Hyperkalemia (hypoaldo)
- Hypomagnesemia (p glycoprotein down with diarrhea)
- Gout
- DM (T>C)
- HTN
- HLD
- TMA
- CsA- hirsutism + gum hyperplasia
- Tacro- alopecia, neuro
CNI Drug Interactions

- Cleared by Cytochrome P450

<table>
<thead>
<tr>
<th>Increase CNI levels</th>
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<tbody>
<tr>
<td>Amiodarone</td>
</tr>
<tr>
<td>ART boosting agents (eg, ritonavir, cobicistat)</td>
</tr>
<tr>
<td>Azole antifungals (eg, fluconazole, posaconazole, voriconazole)</td>
</tr>
<tr>
<td>Grapefruit juice</td>
</tr>
<tr>
<td>HIV protease inhibitors (eg, atazanavir, nelfinavir, saquinavir)</td>
</tr>
<tr>
<td>Macrolide antibiotics (except azithromycin)</td>
</tr>
<tr>
<td>Non-dihydropyridine calcium channel blockers</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Decrease CNI levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiseizure drugs, enzyme-inducing (eg, carbamazepine, fosphenytoin, oxcarbazepine, phenobarbital, phenytoin, primidone)</td>
</tr>
<tr>
<td>Enzalutamide</td>
</tr>
<tr>
<td>Nafcillin</td>
</tr>
<tr>
<td>Rifamycins (eg, rifabutin, rifampin, rifapentine)</td>
</tr>
<tr>
<td>St. John’s wort</td>
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Antiproliferatives

- MMF or AZA

- Careful:
  - Leukopenia
  - GI symptoms (MMF)
  - Drug Interaction of Note: AZA + Allopurinol → severe marrow suppression
Belatacept

- Inhibits T cell activation through costimulation blockade
- No known nephrotoxicity or adverse CV effects
- IV Q2-4 weeks
- $$$
- EBV
Pop Quiz

- What is the most common cause of kidney transplant failure?

- Mortality has not improved much in active Transplant pts

NIDDK
Causes of death in kidney transplant patients
HTN

- Target BP 130/80 (no real data)
- CaChB - may reduce CNI induced vasoconstriction
  - Non-DHP will raise CNI levels
- BB may reduce CV mortality
- ACE/ARB
  - Retrospective study
  - Risks:
    - High K
    - Anemia
    - Transplant RAS/Rejection
    - Confounding rise in Cr
HLD- STATINS

- ALERT Trial- AJT 2005
  - Fluvastatin 80 v placebo
  - LDL levels lowered
  - RCT

- Fluvastatin
- Atorvastatin
- Pravastatin
- (others can interact with CNIs)
Statin adjuncts

- Not well studied and all have risks/SEs
  - Zetia
    - Can interact with CNI (Vytorin)
    - GI SEs
  - Fibrates
    - Rhabdo risk
  - Cholestyramine
    - CNI interactions
  - Fish Oil
    - No data
DM

- 25% of pts have DM at time of txplt
- 25% of txplt pts develop NODAT within 3 years
- Culprit: tacrolimus (esp. if also on prednisone)
Worse allograft and patient survival:

- NODAT conferred RR 3.8 for allograft failure (48% vs 70% after 12y)
- RR 1.5-3 for CV mortality
NODAT

- Tacrolimus
  - Decreased insulin secretion
  - Insulin resistance

- Treatment
  - Lifestyle modifications
  - Insulin usually needed
  - *Metformin should be okay
CVD after transplant

- Txp lowers CV mortality (4x) vs HD but not general pop.
CVD different in transplant patients?

- Different RFs?
  - HPT, phos, time on HD, LVH, wide PP?

- Medial vessel wall concentric calcification
  - Vs traditional atherosclerosis/plaque
  - More pulm HTN, LVH, dCHF, wide PP
  - Increased arterial stiffness
Cancer (USRDS)

- **RR >90**
  - Non-melanoma skin
- **RR 20-90**
  - Kaposi’s Sarcoma
  - Lymphoma
  - Uterine, Cervical, Vulvovaginal
- **RR 5-20**
  - Kidney
  - CNS
  - Melanoma
  - Leukemia
  - Larynx/Mouth
  - Endocrine
  - Hepatobiliary

- **RR 2-5**
  - Breast
  - Prostate
  - Lung
  - Colon
  - Esophagus
  - Pancreas
  - Ovary
  - Testis

3 years post transplant:
- 7.5% get skin cancer
- 7.5% get other cancers
Cancer screening recs

- Age appropriate cancer screening
  - Scope, PAP, testicular self exam, prostate/PSA, mammogram
- Renal US (native kidneys) annually
- Annual derm visits
Vaccines

- Avoid LIVE ATTENUATED vaccines after transplant:
  - Zoster, MMR, HPV, Yellow Fever

- Post Transplant
  - Flu every year
  - PNA every 5 years
  - TDAP every 10 years
  - HAV/HBV if not done already on HD
Posttransplant Infections

- Rate of infection actually REDUCED 4x with a transplant compared to HD

- Highest risk early on post transplant with higher doses of immune suppression
  - Post transplant prophylaxis

- Common things are common!
  - PNA/URI/UTI
Viral Infections

- CMV
  - Know “CMV status”
    - Did donor have CMV? Did recipient have CMV prior to tx?
    - Risk determines course of valcyte ppx post-op

- BK
  - Increased immunosuppression
  - +SV40 stain on Bx
Infection associated malignancy

- EBV $\rightarrow$ PTLD
- HHV8 $\rightarrow$ lymphoma & KS
- HPV $\rightarrow$ SCC oropharynx, gyn
- HBV/HCV $\rightarrow$ HCC
With better allograft survival rates there are more patients in the community with kidney transplants than ever before.

Always be aware of your patients’ immune suppression and understand side effects and potential drug interactions.

Transplant nephrologists and community physicians will need to work together to manage the multitude of issues that can arise in transplant patients.
Thank you!

- MSD Shadowing Program
- Interested? Contact me!
- marc.richards@gmail.com
- 561-325-1376