Educational Objectives

• Describe evidence supporting increased use of higher KDPI kidneys and optimizing allocation of donor kidneys

• Apply current evidence regarding strategies to individualize and optimize immunosuppressive therapy to prevent chronic rejection and minimize immunosuppressant-associated toxicity

• Identify patients at risk for non-adherence and implement strategies to maximize adherence in patients undergoing kidney transplant

Case Study

• 65-year-old woman, with polycystic kidney disease (PKD) and prior mitral-valve replacement, no other coronary artery dissection (CAD), on waiting list for 2.5 years, expected waiting time in region is ~4 years for her blood type (B). Otherwise healthy. She has no living donors. cPRA = 56.

• Called with a kidney offer.

Case Study (cont)

• Offered a kidney from deceased donor with KDPI 89; 1 DR match, blood type A2

• Deceased donor: 5’6” 180lb AA woman, PMH of HTN for <5 years, DBD due to CVA, terminal Cr 1.1 mg/dL; History of jail time in the past 36 months (no DM, no DCD, HCV negative)

Organ Allocation

Major New Components as of December 4, 2014

• Replaced SCD/ECD with KDPI
• Broader sharing for high KPDI kidneys (>85)
• Longevity matching – donor KDPI to recipient expected post-transplant survival (EPTS)
• Increased priority for sensitized candidates/CPRA sliding scale
• Included pre-registration dialysis time
• Incorporated A2/A2B to B

Overview of Policy

Donor

Recipient

KDPI <=20%

Allocation to those with "longest expected post-transplant survival"

KDPI >20% but <=45%

Allocation first to pediatric list, then according to waiting time

KDPI >45% but <=85%

Allocation according to waiting time

KDPI >85%

Allocation to those who consent (similar to yesterday’s ECD)

Kidney becomes available

All allocation sequences to be based on KDPI

https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf#namedest=Policy_08
Donor and Recipient Factors to Determine Groups

<table>
<thead>
<tr>
<th>KDPI Variables</th>
<th>Candidate Estimated Post Transplant Survival (EPTS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor age</td>
<td>Candidate age</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>Candidate diabetes</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Prior transplant</td>
</tr>
<tr>
<td>Diabetes</td>
<td>ESRD time</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td></td>
</tr>
<tr>
<td>COD CVA</td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>DCD</td>
<td></td>
</tr>
<tr>
<td>HCV</td>
<td></td>
</tr>
</tbody>
</table>

Sequence A
KDPI ≤ 20%
- Highly sensitized 0-ABDRmm
- Prior living donor
- Local pediatric
- Local top 20% EPTS
- 0-ABDRmm (all)
- Local (all)
- Regional pediatric
- Regional (all)
- National pediatric
- National (all)

Sequence B
KDPI >20% but <35%
- Highly sensitized 0-ABDRmm
- Prior living donor
- Local pediatric
- Local top 20% EPTS
- 0-ABDRmm (all)
- Local (all)
- Regional pediatric
- Regional (all)
- National pediatric
- National (all)

Sequence C
KDPI ≥ 35% but ≤ 85%
- Highly sensitized 0-ABDRmm
- Prior living donor
- Local pediatric
- Local top 20% EPTS
- 0-ABDRmm (all)
- Local (all)
- National pediatric
- National (top 20%)
- National (all)

Sequence D
KDPI >85%
- Highly sensitized 0-ABDRmm
- Prior living donor
- Local pediatric
- Local top 20% EPTS
- 0-ABDRmm (all)
- Local (all)
- National pediatric
- National (all)
- National + Regional
- National + Regional
- National + National

Kidney Donor Profile Index (KDPI)

KDPI Variables
- Donor age
- Height
- Weight
- Ethnicity
- History of HTN
- History of diabetes
- Cause of death
- Serum creatinine
- HCV status
- DCD status

Graft Survival and Discard Rates by KDPI

Projected Results

- >8000 additional life years annually
- Increase in transplants to blood type B, PRA>98

Survival Advantage of Kidney Transplant is Maintained in Elderly ≥70 Years

Mortality RR (95% CI) for 2,078 first deceased donor kidney transplant recipients vs 5,667 wait-listed dialysis patients ≥70 years of age

The Risk of NOT Being Transplanted is High in the Elderly

Almost half (46%) of candidates >60 years are projected to die before receiving a DDKTx.

Older candidates are now at significant risk for not surviving the interval in which a deceased-donor transplant would become available.

Should You Take a “High KDPI” Kidney or Wait for a “Better Offer”?

- High-KDPI Kidney
  - Increased short-term but decreased long-term mortality risk
  - Break-even point of cumulative survival at 7.7, 18.0, and 19.8 months post-KTx with survival benefit thereafter (P<0.01 for each comparison)

The Combined Risk of Donor Quality and Recipient Age: Higher-quality Kidneys May Not Always Improve Patient and Graft Survival

- UNOS analysis of 137,311 primary kidney transplant recipients 1995-2010 with follow-up through 2012
- Donor organ quality (by KDPI) was divided into quintiles (very high, high, medium, low, and very low quality)
- Recipients 70-79 years had comparable outcomes if they received low-quality kidneys compared to medium-quality kidneys. (HR death, 1.03, P=0.51; HR graft loss, 1.11; PH 0.19)
- Transplanting medium-quality kidneys into elderly recipients does not provide significant advantage over low-quality kidneys

Peri-operative Risk in Elderly is Dramatically Reduced with Living Donor Transplant

- Elderly recipients of LD, SCD, and ECD transplants vs all wait listed patients ≥65 y/o in the USRDS from 1995-2007
- Categorized patients as low, intermediate, or high risk based on presence of comorbidities (ischemic heart disease, congestive heart failure, stroke, peripheral vascular disease):
  - Zero = Low Risk
  - One = Intermediate Risk
  - Two or Diabetes = High Risk

First Report on the OPTN National Variance Allocation of A/A_B Deceased Donor Kidneys to Blood Group B Increases Minority Transplantation

- Eligibility: Candidates with at least two consecutive, quarterly IgG anti-A titer <1:8.
- Majority of donors were white (86%) and the majority of recipients (61%) were non-white
- Rejection rates equivalent, patient survival equivalent to B to B transplants
- As of April 23, 2015: 30 A/A_B to B transplants performed (vs. 6 in the 5 months before the new KAS policy was implemented)
- Only 3.6% of active B candidates were registered to accept potential A/A_B offers

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Public Health Service (PHS) High Risk Donors: ~10% of Donor Pool

Categories of behavior leading to classification of High Risk Donor:
- **MSM**: men who have had sex with another man in the preceding 5 years
- **IDU**: persons who report nonmedical intravenous, intramuscular, or subcutaneous injection of drugs in the preceding 5 years
- **Hemophiliac**: persons with hemophilia or related clotting disorders who have received human derived clotting factor concentrates
- **CSW**: men and women who have engaged in sex in exchange for money or drugs in the preceding 5 years
- **High Risk Sex**: persons who have had sex in the preceding 12 months with any person described in items 1-4 above or with a person known or suspected to have HIV infection
- **HIV exposed**: persons who have been exposed in the preceding 12 months to known or suspected HIV-infected blood through percutaneous inoculation or through contact with an open wound, non-intact skin, or mucous membrane
- **Incarcerated**: inmates of correctional systems

MSM = men who have sex with other men, IDU = injection drug user, CSW = commercial sex worker, HIV = human immunodeficiency virus


Risk of Window Period Hepatitis-C Infection in High Infectious Risk Donors
Systematic Review and Meta-analysis

- NAT testing reduces the estimated window period (WP) for HCV and HIV infection to 7-10 days

<table>
<thead>
<tr>
<th>Risk Behavior</th>
<th>HIV Risk</th>
<th>% HIV Risk</th>
<th>HCV Risk</th>
<th>% HCV Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDU drug use</td>
<td>1:2600</td>
<td>0.05%</td>
<td>1:313</td>
<td>0.3%</td>
</tr>
<tr>
<td>Men, testing positive for HIV</td>
<td>1:2500</td>
<td>0.04%</td>
<td>1:3333</td>
<td>0.03%</td>
</tr>
<tr>
<td>Commercial sex partner</td>
<td>1:3333</td>
<td>0.03%</td>
<td>1:833</td>
<td>0.12%</td>
</tr>
<tr>
<td>Incarcerated</td>
<td>1:10,000</td>
<td>0.01%</td>
<td>1:12,500</td>
<td>0.008%</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>1:20,000</td>
<td>0.005%</td>
<td>1:25,000</td>
<td>0.004%</td>
</tr>
</tbody>
</table>


HCV Transmission Despite Modern Donor Screening Practices: Risks and Responses

- 3 clusters (3 organ donors defined as PHS high risk, with negative NAT testing) resulted in 6 cases of acute HCV infection in transplant recipients
  - 2 with active IDU, one with a history of IDU
- Advisable to screen recipients of PHS high risk donors for HCV and HIV 1-3 months after transplant
- Recent studies indicate successful eradication of HCV following kidney transplant with direct-acting antivirals (DAA)
  - Need to consider access to DAA


Case Study

- Patient accepts kidney offer
- BMI 33, VSS, on BP meds, warfarin, statin, PPI, cPRA 49
- Admitted for transplant, cold ischemia time 21 hours

Case Study

- Immediate graft function, discharged on day 4 on rATG-tacrolimus, mycophenolate (MPA), prednisone
- Month 1: Developed wound infection, tac C0 range 5-10 ng/mL, MPA 720 bid, prednisone tapered to 10 mg daily, creatinine remained stable (1.2-1.4)
- Month 6: BK viremia on screening, 10K, MPA decreased to 360 bid, prednisone tapered to 2.5 daily

Maintenance Immunosuppression Use in USA, 1998-2011

"Gold-standard" Rationale for multi-agent regimen
- Most efficacious
- More immunological targets
- Permits reduced dosing of each drug, with less drug-specific toxicity
Chapter 1: Induction Therapy

Limitations of induction trials
- No double-blind RCT
- No long-term outcomes
- No approved depleting agent
- Alemtuzumab on the way out
- Variable maintenance Rx
- Limitations of induction trials

Factors Influencing Selection of Therapies
- Established efficacy
  - RCTs
- Immunological risk
  - Highly sensitized
  - African-American
- Medical risk
  - Comorbidities
  - Prior immunosuppressive burden
- Potential drug toxicity
  - CNI
  - Steroid

Factors Influencing Selection of Therapies
- Established efficacy
- Immunological risk
- Medical risk
- Potential drug toxicity

Chapter 2: Initial Maintenance

Immunosuppressive Medications

CNI Minimization
- SYMPHONY
- CTOT-8
- CENTRAL
- CONVERT
- ZEUS

CNI Avoidance
- ORION

CNI Elimination
- ASSET

SYMPHONY: “Low Dose” Tacrolimus 4-7 ng/mL

12-month randomized open-label multicenter trial (n=1645)
4 arms (IL2R induction in “low” arms, MMF/Prednisone for all)

At 12 months:

<table>
<thead>
<tr>
<th>Regimen</th>
<th>GFR (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSA “standard”</td>
<td>57.1</td>
</tr>
<tr>
<td>CSA “low”</td>
<td>59.4</td>
</tr>
<tr>
<td>TAC “low”</td>
<td>65.4</td>
</tr>
<tr>
<td>SRL “low”</td>
<td>59.7</td>
</tr>
</tbody>
</table>


SYMPHONY and CNI Minimization

Drug Trough
- Tac (4-7)
- CSA (100-200)
- CSA (50-100)
- SRL (4-8)

12 months
- 6.4
- 142
- 101
- 7.5

36 months
- 6.5
- 114
- 103
- 7.0

The ORION Study

- Tacrolimus elimination [13 wks]
- Tacrolimus avoidance
- Standard tacrolimus-MMF

RCT (n=443)
1. Tac+Srl: 66% withdrawn
2. Srl-MMF: 60% withdrawn (arm terminated)
3. Tac-MMF: 37% withdrawn

Primary endpoint: 1 year GFR: no difference between groups

Adverse events
- SRL arms had higher rates of:
  - withdrawal from study
  - Acute rejection (15% vs 32% vs 8%)
**Tac Withdrawal in Immunologically Quiescent Recipients (CTOT9)**

- Prospective study, non-sensitized, primary live donor recipients
- rATG-Tac-MMF-prednisone for all, randomized at 6 months to continue, vs Tac withdrawal if DSA neg, no rejection/inflammation on protocol biopsy
- 14 weaned, 6/14 developed rejection, 5/14 developed DSA


**CNI Elimination Studies with mTOR Inhibitors**

<table>
<thead>
<tr>
<th>Study</th>
<th>Time to conversion (months)</th>
<th>Follow-up (months)</th>
<th>Baseline CNI</th>
<th>GFR (mL/min)</th>
<th>Treatment Failure/ Graft Loss</th>
<th>IPAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONVERT (Srl)1</td>
<td>6-120</td>
<td>12</td>
<td>CycA or Tac</td>
<td>+4.9</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>ZEUS (Evr)2</td>
<td>4.5</td>
<td>36</td>
<td>CyA</td>
<td>+7.8</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>CENTRAL (Evr)3</td>
<td>2</td>
<td>12</td>
<td>CyA</td>
<td>+8.0</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>ORION (Srl)4</td>
<td>3</td>
<td>12</td>
<td>Tac</td>
<td>-</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>SPARE THE NEPHRON (Srl)5</td>
<td>1-6</td>
<td>24</td>
<td>80% Tac</td>
<td>+3.6</td>
<td>- (but 27% back to CNI)</td>
<td>-</td>
</tr>
</tbody>
</table>


**Belatacept and CNI-Avoidance**

**BENEFIT and BENEFIT-EXT**
- Simultaneous studies: Bela vs CyA
- EXT: ECD, DCD, and prolonged cold time

**What Are the Concerns about Belatacept?**

- Higher rejection rates
- Histologically more severe rejection
- Post-transplant lymphoproliferative disorder risk
- IV administration and cost
- Patient reluctance
- No RCTs with tacrolimus as comparator agent

**Early Steroid Withdrawal RCT**

**Summary at 5 Years**

- 60-month randomized controlled, double-blinded, double-dummy, multicenter trial (n=386)
- 2 arms, rATG-Tac-MMF: steroid withdrawal within 7 days

- Lipids a little better
- No differences in:
  - CV risk
  - weight gain
  - new diabetes
  - kidney function
- Increased
  - acute rejection
  - chronic graft dysfunction

**Case Study (cont)**

- Month 6 to year 2: BK virus clears; stable kidney function (Cr 1.2-1.4) (monthly-quarterly follow-up) with tac trough trending lower (range 3-7 ng/mL)
- Consistent complaints of emotional lability, insomnia, tremor
- At 2-year visit: she asks if she can decrease tacrolimus (level is 3.3 ng/mL despite no changes in dose); also informs you that sometimes she falls asleep before her evening med
Once-a-Day Tacrolimus

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tac-MR*</th>
<th>LCP-Tac*</th>
</tr>
</thead>
<tbody>
<tr>
<td>C0</td>
<td>Similar</td>
<td>Similar</td>
</tr>
<tr>
<td>Cmax</td>
<td>Similar</td>
<td>Lower</td>
</tr>
<tr>
<td>Tmax</td>
<td>Similar</td>
<td>Delayed</td>
</tr>
<tr>
<td>AUC</td>
<td>Lower</td>
<td>Higher</td>
</tr>
</tbody>
</table>

Required dose: Higher for LCP-Tac.

*compared to twice-daily tacrolimus

Efficacy of Once-daily Tacrolimus

- Phase III, open-label, comparative, non-inferiority study
- 638 subjects receiving de novo kidney transplants were randomized to one of three treatment arms: daily tacrolimus extended-release, twice-daily tacrolimus, or twice-daily cyclosporine
- All subjects received basiliximab induction, mycophenolate mofetil, and corticosteroids


Efficacy of LCP-Tacrolimus

- Phase III, RCT, double-blind, double-dummy, primary endpoint: treatment failure
- 543 subjects receiving de novo kidney transplants were randomized to one of two treatment arms: daily LCP-tacrolimus, twice daily tacrolimus
- All subjects received basiliximab induction, mycophenolate mofetil, corticosteroids per local practice

Case Study (cont)

- Converted to tacrolimus MR4; month 26: serum creatinine 1.5 mg/dL; Tac level 5.1 ng/mL, despite stable dose; BK negative
- Month 36: kidney function has declined (Cr 1.9 mg/dL); urine protein/creatinine 1.6, Tac level 2.3 ng/mL, despite stable dose
- Also informs you that she stopped her prednisone 9 months ago because of fear of side effects
- New DSA to DQ at 4500 MFI

Improving Long-term Kidney Allograft Survival

Progress in graft outcomes is due to improved short-term outcomes

Adjusted Rate of Allograft Failure in the USA

Patients aged ≥18 years at transplant; adjusted by age, gender, and race

A Patient for Every Kidney
Optimizing Opportunities and Outcomes in Kidney Transplantation

Graft Survival in DeKAF
Impact of Diagnosis of CAN or CNI Nephrotoxicity
CAN Does not Predict Subsequent Graft Failure: DEKAF Study
- n=440 "troubled grafts"
- Baseline creatinine <2 mg/dL
- Creatinine increase >25%

Late Graft Loss: A Changing Paradigm
- Chronic rejection is the most frequent cause of death-censored graft loss
- Chronic rejection is commonly due to insufficient immunosuppression
  - Inappropriate prescription (minimizing or avoidance strategies)
  - Patient non-adherence

Strategies to Optimize Adherence
- Monitoring drug levels
- Tracking pharmacy refills
- Supervised medication administration
- Electronic notification (patient, center, other)
  - Bottle caps
  - Pill dispensers
  - Apps
  - Alarms/reminders
- Simplified regimens

Why Do Kidneys Fail? Mayo Experience
1996-2006: 330 of 1317 KTX with graft loss at mean 50-month follow-up
138 (43.4%) due to death
39 (11.8%) due to 1° non-function
153 (46.3%) due to graft failure (biopsies mean 4.7 months prior to graft loss)

- Of "IF/TA"
- ¼ history of acute rejection
- Of "glomerular disease"
- 45% "transplant glomerulopathy" (~HLA Ab?)
- ONLY 1 GRAFT LOSS ATTRIBUTED SOLELY TO CNI TOXICITY

The Role of Antibody-mediated Rejection and Non-adherence in Kidney Transplant Failure
- Identification of Antibodies in Transplant Failure
- IF/TA (21%)
- Glomerular disease (27%)
- Acute rejection (24%)

Transplant Outcomes and Economic Costs Associated with Patient Noncompliance to Immunosuppression
- Use of Medicare claims data to calculate compliance as medication possession ratio (MPR)
- 15,525 KTx recipients with at least 1 year of graft function

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Transplant Outcomes Associated with Patient Noncompliance to Immunosuppression

Medication possession ratio quartile cutpoints:

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Y1</th>
<th>Y2</th>
<th>Y3</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>25%</td>
<td>0.731</td>
<td>0.816</td>
<td>0.827</td>
<td>0.811</td>
</tr>
<tr>
<td>50%</td>
<td>0.936</td>
<td>0.961</td>
<td>0.962</td>
<td>0.951</td>
</tr>
<tr>
<td>75%</td>
<td>0.964</td>
<td>0.997</td>
<td>1.000</td>
<td>0.998</td>
</tr>
</tbody>
</table>

Compliance by quartiles:

- **Excellent** (Ref.)
  - HR: 1.00, P: 0.99
- **Good**
  - HR: 1.00, P: <0.0001
- **Fair**
  - HR: 1.00, P: <0.0001
- **Poor**
  - HR: 1.00, P: <0.0001


Predictive Patterns of Early Medication Adherence in Renal Transplantation

MEMS (Medication Event Monitoring System): A microprocessor embedded in the cap of a medication bottle records every opening and closing of the cap.

- **195 patients:**
  - 44 (22.6%) decreased adherence by 7% or more in month 2 post treatment
    - **Acute Rejection**
    - **Early Graft Loss**

Use of Drug Level Monitoring (Intra-patient Variability) to Assess Under-immunosuppression/adherence

- 356 patients, measured tacrolimus variability while on stable dose (\(\text{tacSD} = \text{tacrolimus standard deviation}\)), median follow-up 3.72 years
- Composite end point: late allograft rejection, transplant glomerulopathy, or graft loss (including death)

- For every 1-unit increase in TacSD, a 27% increase in composite end point
  \(\text{HR} 1.27 (95\% \text{CI} 1.03-1.56)\)


Persistence and Adherence in Kidney Recipients: Effect of Dosing Frequency

- 219 patients randomized to once-daily tacro or twice-daily tacro 035.

<table>
<thead>
<tr>
<th>Dosing Frequency</th>
<th>Persistence, 6 mos</th>
<th>Adherence, 6 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once-daily (n=145)</td>
<td>82%</td>
<td>88%</td>
</tr>
<tr>
<td>Twice-daily (n=74)</td>
<td>72%</td>
<td>79%</td>
</tr>
<tr>
<td>(P) value</td>
<td>0.08</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

\(P\) values for differences in adherence and persistence between groups:
- Doses were missed more frequently in the evening than in the morning (11.7% vs 14.2%; \(P=0.0035\))


Difficulty for Both Prediction and Intervention

- There is not one single cause for non-adherence
  - Examples
    - Lack of understanding of the regimen
    - Forgetfulness
    - Financial problems with co-pays
    - Difficulty with regimen (work schedule/travel)
  - Therefore, it is difficult to have a single effective intervention

Outcomes of Interest to Patients:

- **Bone disease/joint pain**
- **Skin thinning**
- **Hair loss**
- **Dry mouth**
- **Hand tremor/shaking**
- **Gastrointestinal (diarrhea, nausea, stomach pain)**
- **Puffy face**
- **Weight gain**
- **Fatigue**
- **Infections**
- **Swollen gums**
- **Swollen face** (and acute rejection, graft, and patient survival)

Conclusions

- Anticipated benefits of the new kidney allocation system include improved equity and utility
- Compared to remaining on dialysis for better quality organs, high KDPI kidneys and kidneys from PHS-increased donors are associated with better outcomes in patients who are older or are residents in regions with longer waiting times
- Among currently used immunosuppressants:
  - tacrolimus-based therapy remains the efficacy “gold standard”
  - belatacept is an emerging alternative, though trials comparing it to tacrolimus-based therapy are needed
- The leading cause of death-censored graft loss is chronic rejection, typically due to non-adherence
- Several strategies to improve adherence are entering the transplant arena, including use of more simplified immunosuppression regimens

CME Credit

- Post-activity Survey
  – Now that the program has completed, please take a moment to answer the Post-activity Survey questions on your form
  – Your answers are important and will help us identify remaining educational gaps and shape future CME activities
- CME Evaluation
  – If you’re seeking credit, ensure you’ve filled in your name and demographic information on page 1 and complete the CME Evaluation on your form (after the Post-activity Survey)
  – Return all forms to on-site CME staff
  
  Thank you for joining us today!