Transplant Nephrology Update: Focus on Outcomes and Increasing Access to Transplantation

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Medical Director, Kidney and Pancreas Transplant Programs
Objectives:

• Describe trends in kidney transplant outcomes with a view to educating patients and their families
• Describe the growing use of pair donor exchange as a way to enhance the availability of living donation transplant to those with blood group and tissue incompatibility
• Describe how to maintain wellness among former kidney donors
Likelihood of Dying While Awaiting Transplant

Patients age 18 & older, listed for a first-time kidney or kidney-pancreas transplant.
Waiting Time Determines Transplant Outcome

Survival Advantage of Transplantation

How long will my kidney go?

Figure 2: Actuarial (diamond marker, solid line) and projected (round marker, dotted line) cumulative half-lives. (A) First SCD deceased versus first living donor and (B) first SCD deceased black versus nonblack recipients.
Matching Remains Relevant
Long Term Outcomes Similar Across Most CNI anchored regimens


1954: First Successful Live Donor Kidney Transplant:
Drs. Joseph E. Murray, Hartwell Harrison, David Hume, and John Merril perform the first successful kidney transplant at Peter Bent Brigham Hospital (now Brigham & Women's Hospital) in Boston.

The transplant is from Ronald Herrick into his identical twin Richard.
Richard Herrick lives for another eight years

Murray goes on to become one of the co-winners of the 1990 Nobel Prize in Physiology or Medicine along with E.Donnel Thomas "for their discoveries concerning organ and cell transplantation in the treatment of human disease."
Characteristics of the Low-Risk Subgroups in the General Population Cohorts.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk population — no. of participants</td>
<td>387 (87)</td>
<td>515 (78)</td>
<td>1,362,305 (7)</td>
<td>2,310,417 (7)</td>
</tr>
<tr>
<td>Total calendar year</td>
<td>2015-16</td>
<td>2015-16</td>
<td>2015-16</td>
<td>2015-16</td>
</tr>
<tr>
<td>Eligible male — no. of participants (%)</td>
<td>38 (30)</td>
<td>51 (30)</td>
<td>2,263 (12)</td>
<td>1,221 (12)</td>
</tr>
<tr>
<td>P value</td>
<td>0.01</td>
<td>0.01</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

50 Years Later.....Ronald Herrick and Joseph Murray, MD
Risk Factors for ESRD after Living Donation

- Black race (hazard ratio [HR], 2.96; 95% confidence interval [95% CI], 2.25 to 3.89; \( P<0.001 \)) and male sex (HR, 1.88; 95% CI, 1.50 to 2.35; \( P<0.001 \)) was associated with higher risk of ESRD in donors.

- Among nonblack donors, older age was associated with greater risk (HR per 10 years, 1.40; 95% CI, 1.23 to 1.59; \( P<0.001 \)).

- **Among black donors, older age was not significantly associated with risk (HR, 0.88; 95% CI, 0.72 to 1.09; \( P=0.3 \)).**

- Greater body mass index: (HR per 5 kg/m\(^2\), 1.61; 95% CI, 1.29 to 2.00; \( P<0.001 \)).

- Donors who had a first-degree biological relationship to the recipient: (HR, 1.70; 95% CI, 1.24 to 2.34; \( P<0.01 \)).
Overall, numbers of living donors progressing to ESRD are small

- Predicted 20-year risk of ESRD for the median donor was only 34 cases per 10,000 donors, but 1% of donors had predicted risk exceeding 256 cases per 10,000 donors.
Kidney-Failure Risk Projection for the Living Kidney-Donor Candidate

Study Overview

• This study examined risk associations calibrated to the U.S. population-level incidence of end-stage renal disease and death and projected long-term incidences of ESRD.

• Risk projections among nondonors were lower than 15-year observed risks after donation.
Projections of the Incidence of End-Stage Renal Disease (ESRD) in the United States According to Age, Race, and Sex for the Base-Case Scenario.

Meta-Analysis of Multivariable-Adjusted Hazard Ratios That Estimate the Association of Baseline Characteristics with ESRD.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard Ratio (95% CI)</th>
<th>p&lt;.05</th>
<th>Population Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR per decrease of 15 ml/min/1.73 m²</td>
<td>6.61 (4.87-8.96)</td>
<td>1.80 (1.50-2.15)</td>
<td>0.66 (0.56-0.7)</td>
</tr>
<tr>
<td>≤&lt;60 ml/min/1.73 m²</td>
<td>1.61 (1.33-1.97)</td>
<td>0.49 (0.43-0.57)</td>
<td>1.72 (1.56-1.93)</td>
</tr>
<tr>
<td>60-89 ml/min/1.73 m²</td>
<td>1.01 (0.32-1.21)</td>
<td>0.02 (0.02-0.03)</td>
<td>1.27 (1.13-1.41)</td>
</tr>
<tr>
<td>90-110 ml/min/1.73 m²</td>
<td>0.78 (0.56-1.10)</td>
<td>-0.24 (0.09-0.15)</td>
<td>0.72 (0.54-0.97)</td>
</tr>
<tr>
<td>≥120 ml/min/1.73 m²</td>
<td>0.74 (0.56-1.03)</td>
<td>-0.24 (0.09-0.15)</td>
<td>0.72 (0.54-0.97)</td>
</tr>
<tr>
<td>Systolic blood pressure, per increase of 20 mm Hg</td>
<td>1.42 (1.27-1.58)</td>
<td>0.35 (0.4-0.7)</td>
<td>1.77 (1.73-1.8)</td>
</tr>
<tr>
<td>Antihypertensive drug use</td>
<td>1.35 (0.01-1.82)</td>
<td>0.36 (0.15-1.31)</td>
<td>1.17 (0.74-1.88)</td>
</tr>
<tr>
<td>Non-insulin-dependent diabetes mellitus</td>
<td>3.11 (1.51-6.74)</td>
<td>1.10 (0.23-5.35)</td>
<td>2.95 (0.92-8.88)</td>
</tr>
<tr>
<td>Body-mass index, per 5-point increase ≤&lt;30</td>
<td>0.98 (0.81-1.2)</td>
<td>-0.02 (0.01-0.03)</td>
<td>1.20 (1.15-1.25)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>1.16 (0.76-1.78)</td>
<td>0.35 (0.05-0.24)</td>
<td>1.20 (0.95-1.55)</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Former smokers</td>
<td>1.45 (1.25-1.71)</td>
<td>0.57 (0.3-0.98)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>1.76 (1.29-2.42)</td>
<td>0.57 (0.3-0.98)</td>
<td>1.75 (1.02-3.0)</td>
</tr>
<tr>
<td>Urinary albumin-to-creatinine ratio, per increase of 10%</td>
<td>2.94 (0.95-8.73)</td>
<td>1.08 (0.55-2.16)</td>
<td>5.48 (2.37-12.71)</td>
</tr>
</tbody>
</table>

*p CI denotes confidence interval, and SE standard error. The analysis was additionally adjusted for age, race, and sex. The reference category for use of antihypertensive drugs was no use of antihypertensive drugs. The reference category for non-insulin-dependent diabetes mellitus was no diabetes. The reference category for smoking status was never smoked."
Projected Incidence of ESRD in the United States among Hypothetical Donor Candidates in the Absence of Kidney Donation.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Age</th>
<th>Race</th>
<th>eGFR</th>
<th>Urinary Albumin: Creatinine Ratio†</th>
<th>Systolic Blood Pressure</th>
<th>Smoking Status</th>
<th>15-Yr Projection (95% CI)</th>
<th>Model-Based Lifetime Projection (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>Black</td>
<td>115</td>
<td>4</td>
<td>130</td>
<td>Never</td>
<td>0.1 (0.1–0.1)</td>
<td>1.9 (1.2–2.5)</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>Black</td>
<td>115</td>
<td>4</td>
<td>130</td>
<td>Current</td>
<td>0.2 (0.1–0.2)</td>
<td>3.4 (2.0–4.8)</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>Black</td>
<td>115</td>
<td>4</td>
<td>140ζ</td>
<td>Current</td>
<td>0.3 (0.1–0.4)</td>
<td>5.4 (2.9–8.5)</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>Black</td>
<td>115</td>
<td>30</td>
<td>140ζ</td>
<td>Current</td>
<td>0.7 (0.2–1.5)</td>
<td>13.3 (4.8–27.0)</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>White</td>
<td>80</td>
<td>4</td>
<td>140</td>
<td>Never</td>
<td>0.2 (0.1–0.3)</td>
<td>0.4 (0.2–0.6)</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>White</td>
<td>60</td>
<td>4</td>
<td>140</td>
<td>Never</td>
<td>0.4 (0.2–0.6)</td>
<td>0.7 (0.3–1.2)</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>White</td>
<td>60</td>
<td>4</td>
<td>140ζ</td>
<td>Never</td>
<td>0.5 (0.2–0.8)</td>
<td>1.0 (0.5–1.7)</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>White</td>
<td>60</td>
<td>30</td>
<td>140ζ</td>
<td>Current</td>
<td>2.2 (1.1–3.6)</td>
<td>4.4 (2.1–7.0)</td>
</tr>
</tbody>
</table>

* The online risk tool is available at www.transplantmodels.com/esrdrisk. Lifetime projections are based on 15 years of follow-up data and calibrated to the incidence of ESRD in the U.S. low-risk population; thus they are imprecise. All estimates reflect the population average for unmeasured characteristics; individual risk may be higher or lower. Projections shown are for a man with the specified characteristics and with a BMI of 25 and no diabetes. Confidence intervals were obtained from simulations sampled from the distribution of hazard ratios in the meta-analysis.

† Urinary albumin-to-creatinine ratio was measured in milligrams of albumin to grams of creatinine.

ζ The projected incidence of ESRD is among persons who are taking antihypertensive medication.

Conclusions

- Multiple demographic and health characteristics may be used together to estimate the projected long-term risk of ESRD among living kidney-donor candidates and to inform acceptance criteria for kidney donors.
Risk of Donation in Sweden Among Closely Related Donors

Mjoen et al, Kidney Int 2014;86:162-67
Precision Medicine Approaches May be Feasible

A Kidney Disease Chip, has been developed and is a potentially useful tool in testing large kindreds

Utility limited by cost

Need to understand allelic variants and formes fruste
Kidney donations from living donors

**Age Distribution**
- 18-34
- 35-49
- 50-64
- 65+

**Sex Distribution**
- Female
- Male

**Race Distribution**
- Black
- Hispanic
- Asian
- Other/unk.
- White

The charts show the trend in kidney donations from living donors across different age groups, sexes, and races from the years 1998 to 2010.
KI 3.2 Kidney transplants from living donors, by donor relation
KI 3.5 Paired kidney donations
Chain Transplantation: Initial Experience of a Large Multicenter Program
Traditional Paired Exchange

- Limited by the reciprocal matching requirement.
  A  X  B
  C  X  D

- This constraint becomes less limiting as paired-exchanges include multiple recipient/donor pairs
Exchange because of Cross-Match Incompatibility and a Blood-Type Incompatibility
Alvin Roth (Nobel Laureate Economics, 2012)

• Cooperative Game Theory to study different matching methods.

• Within the framework of this theory, it is especially important that a stable match is found.

• Alvin Roth used Shapley's theoretical results to explain how markets function in practice.
Chain Transplantation

• The next pair's donor can potentially match any other pair's recipient in the database.
• Lack of reciprocity requirement is the driving force behind chains having superior matching performance
• Allows for improved matching quality and increased quantity of transplantation
Multiple Donor – Recipient Pairs
Chain Transplantation

• Computer algorithm that performs an exhaustive combinatorial search of potential clusters of transplants.

• Clusters: a group of transplants, usually occurring temporally close together. Chains are composed of a series of clusters.

• The first cluster of a chain begins with a Non Directed Donor. Subsequent clusters are linked together using “bridge” donors.

• The “bridge donor”, is a donor who “agrees not to donate his/her kidney at the same time as their loved one receives a kidney, but rather at a later date”. A “renege” occurs if a “bridge donor” becomes unavailable to donate for any reason, including: health issues and changing their mind.

• “Closed” chains end to the wait list, and “open” chains continue indefinitely.
No DGF; median 1-week creatinine of grafts shipped coast-to-coast (1.6 mg/dL) was similar to those not shipped (1.5 mg/dL)
An Overview of Kidney Allocation in the US
KDRI

• Kidney Donor Risk Index: Donor and Transplant factors each independently associated with graft failure or death

• DONOR AGE, DONOR RACE, History of HTN, history of diabetes, serum creatinine, cerebrovascular cause of death, height, weight, donation after cardiac death, HCV status, HLA A-B DR mismatch, cold ischemia time and double or en bloc transplant

Transplantation 2009;88: 231–236)
KDRI and Donor Age

Transplantation 2009;88: 231–236)
Kidney Donor Risk Index (KDRI)

- Transplants of kidneys in the highest KDRI quintile (1.45) had an adjusted 5-year graft survival of 63%

- When compared with 82% and 79% in the two lowest KDRI quintiles (0.79 and 0.79–0.96, respectively)

*C-statistic: 0.6*

*Transplantation 2009;88: 231–236*
The Kidney Donor Profile Index (KDPI) is a numerical measure that combines ten dimensions of information about a donor, including clinical parameters and demographics, to express the quality of the donor kidneys relative to other donors.

- The KDPI is derived by first calculating the Kidney Donor Risk Index (KDRI) for a deceased donor
- A donor with a KDPI of 90%, for example, has a KDRI greater than 90% of donors in the chosen reference population. Relative risk mapping to a cumulative percentage scale
- The reference population of donors is all deceased donors in the U.S. from whom a kidney was recovered for the purpose of transplantation during the prior calendar year.
- Lower KDPI values are associated with increased donor quality; higher KDPI values are associated with lower donor quality
KDPI- Touted benefits

• 10 variables instead of 4 in the ECD definition
• Continuous rather than dichotomous cutoff
• However, keep in mind that continuous is not that much different from cutoffs when behavior is non-linear
KDPI and Graft Survival
Figure 1: Estimated Graft Half Lives (years)

- Living Donor: 12.48 years
- KDPI 0-20%: 11.44 years
- KDPI 21-85%: 8.90 years
- KDPI 86-100%: 5.60 years
Allocation component changes

1. Waiting time calculation - pre-registration dialysis time added
2. Candidate classification - Estimated Post Transplant Survival (EPTS) score
3. Kidney donor classification - replace SCD/ECD with Kidney Donor Profile Index (KDPI)
4. Priority for sensitized candidates - calculated panel reactive antibody (CPRA) sliding scale
Allocation component changes

5. Blood type eligibility - A2 and A2B to B compatible
6. Pediatric kidney allocation – KDPI priority
Dialysis
Srinivas, Tirpe Rajagopal
276 Bayview Dr
Mount Pleasant SC 294643465

DOB: 05-30-1965
Issued: 05-23-2013
Expires: 05-30-2023
Class: D
Sex: M
Weight: 180
Height: 5-08
District: A
Endorse: None

DL#: 103292566
10065 O 2
Governor

South Carolina
USA
DRIVER'S LICENSE

Palmetto Tree
Mount Pleasant

CLASS: Vehicles not exceeding 26,000 GVW. Includes Class G and trike. Does not include MTC or MTC w/ sidecar.

ENDORSEMENTS
None

ENDORSEMENTS

RESTRICTIONS
A - Corrective Lens

DONOR: YES

1011226500050424