Transplantation

David D Lee, M.D.
# Immune Response to Allograft

<table>
<thead>
<tr>
<th>Cellular</th>
<th>Humoral</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Recognition of foreign antigen</td>
<td>• Recognition of foreign antigen</td>
</tr>
<tr>
<td>• Activation of antigen-specific lymphocytes</td>
<td>• Antibody formation by immune system</td>
</tr>
<tr>
<td>• Graft rejection (cellular-mediated)</td>
<td>• Graft rejection (antibody-mediated)</td>
</tr>
</tbody>
</table>

**SRTR**
Immune system priming

Antigen Presenting Cell (APC)

Co-stimulatory Signal (2)
Antigenic Signal (1)
Cytokine Signal (3)

T-cell receptor
Increased Ca^{2+}
Activated calcineurin
IL-2
IL-2 gene promoter
NFAT
NFAT

T cell proliferation

Cell Cycle
G1 S M G2
Transplantation
All about allocation

David D Lee, M.D.
Imbalance Between Supply and Demand Increases
The Need For Allocation Policy

* Relative organ supply = deceased and living donor organs recovered / waiting list
Organ Allocation

• The organ shortage drives the need for organ sharing, allocation rules, and oversight
• There is no single best method of organ sharing
• Principles of organ sharing
  – Equity
  – Utility
  – Benefit
  – Urgency
• Development of consensus
• Maintaining public trust in a system of voluntary deceased organ donation
• The concept of deceased donor organs as scarce national resources
Organ Allocation Geography

58 DSAs/OPOs

11 Regions
Allocation Framework - NOTA

- The act called for the formation of the Organ Procurement and Transplantation Network (OPTN) to be operated by a private, non-profit organization under federal contract.
- OPOs must have a system to allocate organs
  - equitably among transplant patients (not centers)
  - according to “established medical criteria”
- OPTN shall establish medical criteria for allocating organs and assist OPOs in nationwide equitable distribution among patients
  - medical criteria, not social or economic criteria
- OPO service area of sufficient size to assure equitable distribution of organs
- Special consideration for children and highly sensitized
Federal Final Rule

October 20, 1999 Section 121.8
Amendments to National Organ Transplant Act of 1984

- Organ-specific
- Sound medical judgment
- Best use of organs
- Give programs the right to refuse
- Avoid wastage and futile transplants
- Promote patient access
- Promote efficient organ placement
- Not to be based on candidate’s location unless to do otherwise would result in inefficient placement, wasted organs, poor use of organs...
Creating National Transplant Policy

ISSUE

Transplant Community

OPTN Committees

Public Comment

OPTN Board of Directors

Secretary of Health and Human Services

POLICY
How would you design the best organ allocation system?
Approaches to allocation

- **Equity: Fairness**
  - Let waiting time accumulate and allow candidates to move up the list
- **Urgency**
  - Sickest first
  - Minimize waitlist deaths
- **Utility:**
  - Maximize donor utilization
  - Maximize life of organ
- **Benefit:**
  - Optimize outcomes following transplantation
  - Maximize added life to recipient
Should everyone receive a transplant?

- Futile transplant—some patients with end organ failure may do better with alternative therapy
- Lung transplantation—almost half of the patients listed were de-listed when a benefit-based schema was instituted
- Low MELD score
- 300,000 people on dialysis and only 110,000 are on the UNOS kidney waiting list
Should we include an outcome measure?

• Realization that some candidates do better with certain types of organs than others—i.e. the right organ for the right recipient
• Balance outcome with equal access to transplant (utility vs justice)?
• Stewardship?
• Some Donor Families might want to maximize the benefit of the transplant
• To comply with the Federal Final Rule
• How would you measure outcome in organ transplantation?
Possible Outcome Measures

- Improved quality of life
- Decreased wait list mortality
- Improved graft survival
- Improved patient survival
- Life years from transplant
Liver

How is this done?
Liver Allocation

• Sickest first (urgency)
  – Who is the sickest?

• Evolution of an Urgency Based Approach
  – Status
  – Child Turcotte Pugh (CPT) score
  – MELD

• Advantages of MELD/PELD
  – Uses more objective and verifiable data
  – More reflective of risk of mortality
  – Less dependent on wait time
Liver Waitlist Deaths and Death Rate?
Impact of MELD/PELD

Source: Scientific Registry of Transplant Recipients
Mortality Rates by MELD

<table>
<thead>
<tr>
<th>MELD</th>
<th>Waitlist Rate per 1000 PY</th>
<th>Transplant Rate per 1000 PY</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-11</td>
<td>HR=3.64 P&lt;0.001</td>
<td>45</td>
</tr>
<tr>
<td>12-14</td>
<td>HR=2.35 P&lt;0.001</td>
<td>53</td>
</tr>
<tr>
<td>15-17</td>
<td>HR=1.21 P=0.41</td>
<td>127</td>
</tr>
<tr>
<td>18-20</td>
<td>HR=0.62 P&lt;0.01</td>
<td>146</td>
</tr>
<tr>
<td>21-23</td>
<td>HR=0.38 P&lt;0.001</td>
<td>165</td>
</tr>
<tr>
<td>24-26</td>
<td>HR=0.22 P&lt;0.001</td>
<td>272</td>
</tr>
<tr>
<td>27-29</td>
<td>HR=0.18 P&lt;0.001</td>
<td>174</td>
</tr>
<tr>
<td>30-39</td>
<td>HR=0.07 P&lt;0.001</td>
<td>515</td>
</tr>
<tr>
<td>40+</td>
<td>HR=0.04 P&lt;0.001</td>
<td>10000</td>
</tr>
</tbody>
</table>
Transplant Benefit by MELD: Box Plots

Transplant benefit (years)

MELD

Schaubel, D et al
MELD - Limitations

- MELD not predictive of all mortality
  - e.g. Liver Intestine candidates
  - Impact of other events associated with chronic liver disease (e.g. SBP)
  - HCC
    - Risk of drop out (and subsequent mortality) not captured in MELD
  - Other diseases where burden not well captured by MELD
    - Metabolic Diseases (e.g. hyperammonemia)
    - Familial Amyloid Polyneurpathy
    - Hepatopulmonary Syndrome, Portopulmonary Syndrome

- Therefore need exceptions
  - Exceptions function as a mechanism to prioritize patients in an allocation system where the primary determinant (MELD) appears to not function well
Exceptions to MELD and PELD

Transplants per year

Total Exceptions: 28% 28% 29% 28% 29% 32%

Source: Scientific Registry of Transplant Recipients
Rising number of requests for MELD exception

Figure 2: Rate of exception requests by initial listing year, with 2002 as reference year.
Study: Liver donations in South Carolina would be sent to patients in the Northeast under new proposal

In a turf battle for organs, a policy review rattles the national transplant

Liver transplant distribution changed after years of debate
Kidney

What is different about kidney than liver?
Evolution of Kidney Allocation Policy

Waiting Time
2 words

Current Policy
7,551 words
Potential Factors in Kidney Allocation

- Waiting time*
- Outcome
- Matching*
- Sensitization*
- Age (donor/recipient)
- Quality of life
- Urgency
- Geography*
- Burden of disease
- Cold ischemia time
- Previous kidney transplant
- SPK*
- A₂/A₂B → B system
- WT from initiation of dialysis*
- Efficiency and cost of system

*part of current system
Figure 5. Deceased Donor Transplantation Rate* Among Kidney Waiting List Patients by State, 1996-2005

*Adjusted for age, race, ethnicity, sex, ESRD cause, wait-list year, comorbid conditions, insurance type, blood type, PRA, and HLA; Censored at death, living donor transplant or end of study; Compared to National average of 1.00; 58,298 of 159,279 received a deceased donor transplant.

Ways to accommodate everyone who benefits

• Living donors
• Allocating donors with shorter life expectancies to candidates with shorter life expectancies
• “The right kidney for the right recipient” applies to both living and deceased donors
Current Deceased Donor Kidney Allocation Algorithm

- Allocates ECD kidneys (15%) based upon waiting time alone

- Allocates SCD (85%) kidneys
  - kidney plus extrarenal organ
  - zero HLA-A,B,DR mismatched candidates
  - HLA mismatched candidates based upon a point system
  - Prior living donors
  - Children under age 18 (first chance at organs from donors under the age of 35)
  - As payback from debtor OPOs to creditor OPOs, local OPO, regional OPO, national OPO, debtor OPO
Current Deceased Donor Kidney Allocation Point System

• Waitlisting (1 point)
• Time waiting (1 point per year, fraction of a point for partial year)
• Prior sensitization (4 points for Panel Reactive Antibody level $\geq$ 80%)
• HLA Similarity (2 points zero HLA-DR MM, 1 point for a one HLA-DR MM)
Ongoing Criticisms of the Kidney Allocation Algorithm

• Contributes to system-wide inequities in access
  – Race, ethnicity, socioeconomic status
  – Geography
• Time consuming, leads to inefficient allocation and prolonged cold ischemic injury
• Does not account for medical needs of candidates (except for pediatric and SPK candidates)
• Does not (with the exception of ECD) account for differences in potential survival of recipients and donated organs
Percent of Recipients Dying with Functioning Graft Increases with Age

% DWFG, Assumes Complete Ascertainment

- **10-year (1987-1997 transplants)**
- **5-year (1987 - 2002 transplants)**
- **3-year (1987 - 2004 transplants)**

Additional ascertainment of death and graft failure from SSDMF, CMS.
Figure 4. Histogram of KDRI by ECD Status

Rao, Transplantation 2008
Current concept

• The top 20% of kidneys (as defined by KDPI) are allocated first to the top 20% of candidates (as defined by estimated post transplant survival).

• All other kidneys (those with a KDPI score >20%) are allocated to candidates within 15 years (older and younger) of the age of the donor.

• Minimizes
  – the risk of retransplantation in recipients with longer expected lifetimes
  – death with graft function in those with shorter expected lifetimes.
Pancreas
Deceased donor pancreas transplant rates

Stegall et al., Transplantation 2007
Factors Influencing Pancreas Allocation Rules

- Older and obese donor pancreata rarely used for whole organ transplant.
- CIT requirements for whole pancreas and islets make post-recovery placement difficult.
- Survival benefit of SPK greater than PAK/PTA, although specific benefit of the pancreas arguable.
- Solitary pancreata more difficult to place compared with SPK but more easily shared.
- SPK transplants take kidneys from KTA candidates.
National Pancreas Allocation

- Mandatory sharing of 0MM to sensitized candidates (CPRA > 80)
  - 0MM Kidney-pancreas (local -> regional -> national) then
  - Pancreas (MM local) then
  - 0MM pancreas (local -> regional -> national)
- Donor < age 50 AND BMI < 30
  - Pancreas: local rules -> regional -> national then
  - Islets: local -> regional -> national
- Donor > age 50 OR BMI > 30
  - Pancreas: local rules then
  - Islets: local -> regional -> national then
  - Pancreas: regional -> national
  - Variances which use this algorithm for all donors
- Kidneys may be shared with pancreas but no obligation to do so (except 0MM)
- Accrued waiting time for kidney can be applied to pancreas, but NOT vice versa
Current Pancreas Allocation Policy

- ~66% of pancreata are allocated to SPK candidates.
  - 77% are <50 yrs of age (44% of adults for KI).
  - No medical qualifying criteria for status of diabetes.

- OPOs may choose whether SPKs precede or follow KI candidates, such as pediatric kidney candidates.

- No uniform national system for allocating pancreata:
  - Some DSAs require the pancreas to follow the kidney
  - Most DSAs allow the kidney to follow the pancreas
    - Most have separate SPK and PA lists
    - Some have a combined list (SPK and PA)
Whole Pancreas Allocation is Influenced by Local Kidney Allocation Rules

• **SPK vs. KTA**
  - **Kidney follows the pancreas**
    • Pancreas recipient receives kidney irrespective of kidney match run status
    • Increases pancreas utilization
    • Consistent with other multiorgan transplant (heart-kidney, liver-kidney)
    • Proposed kidney allocation scheme uses this nationally
  - **Limited “higher priority” KTA candidates: Peds, sensitized**
  - **Pancreas follows the kidney**
    • SPK recipient must be at top of kidney match run
    • Severely limits SPK

**LEGEND**
- **Red**: KI follows PA
- **Green**: PA follows KI
- **Blue**: Mixed
- **Yellow**: No local PA program

No local PA program
Whole Pancreas Allocation is Determined Locally

- **SPK vs. PTA/PAK**
  - SPK gets priority
    - Increases SPK transplant and indirectly pancreas transplant benefit
    - Increases pancreas utilization
  - PTA/PAK gets priority
    - Encourages living donor kidney transplant
    - Reduces drain of kidneys from KTA candidates
  - No priority
    - Determined by waiting time regardless of combined/solitary
  - Alternating priority
Whole Pancreas Allocation is Determined Locally

If the pancreas is allocated first, check all that apply:

- **83.3%** SPK candidates have priority
- **22.2%** Pancreas candidates have priority
- **38.9%** Neither; allocation is based on waiting time
- **27.8%** Certain kidney candidates have priority over SPK candidates
- **22.2%** Other
Summary of Current Pancreas Allocation

- Pancreas allocation is mostly determined by geography and waiting time.
- OPO-specific policies factor heavily in determining kidney allocation to SPK candidates and prioritization of SPK vs PTA/PAK candidates.
- Pancreata from obese and older donors are preferentially allocated to islet transplant candidates after local whole pancreas.
- Variations in allocation policy may significantly influence utilization.
Summary of National Pancreas Allocation Proposal

- Kidney follows pancreas allocation, locally
- Pancreata are allocated to recipients on a combined PA and SPK waiting list
- Consistent SPK qualifying criteria (to accrue SPK waiting time) defining uremia and diabetes for kidney and pancreas transplantation, respectively.
  - Kidney: on chronic maintenance dialysis or GFR or CrCl ≤ 20 mL/min
  - Pancreas: On insulin and C-peptide ≤ 2 ng/mL OR On insulin and C-peptide > 2 ng/mL AND BMI ≤ 30 kg/m²
- Pancreas allocation disentangled from kidney allocation.
Heart & Lung
Heart Allocation

• Based on waiting time within urgency strata
• Local first, then sharing occurs by progressive zones (=500 miles)
• **Status 1A**
  – ventilator
  – balloon pump
  – swan with high dose single or lower dose multiple inotropes
  – total artificial heart
  – VAD with evidence of mechanical failure or infection (plus all VADs get 30 days to be used at the discretion of the center)
  – Other occasional exceptions
• **Status 1B**
  – inotropes at lower doses without a swan
  – VAD not meeting the criteria above (or also rarely exceptions)
• **Status 2:** everyone else.
Previous Heart Allocation system based on waiting time within urgency and geography strata

- Local
  1. Status 1A
  2. Status 1B
  3. Status 2
- Zone A
  4. Status 1A
  5. Status 1B
- Zone B
  6. Status 1A
  7. Status 1B
- Zone A
  8. Status 2
- Zone B
  9. Status 2
- Zone C
  10. Status 1A
  11. Status 1B
  12. Status 2
- Zone D
  13. Status 1A
  14. Status 1B
  15. Status 2
Current Heart Allocation system based on waiting time within urgency and geography strata (modified 2006)

- Local
  - 1. Status 1A
  - 2. Status 1B
- Zone A
  - 3. Status 1A
  - 4. Status 1B
- Local
  - 5. Status 2
- Zone B
  - 6. Status 1A
  - 7. Status 1B
- Zone A
  - 8. Status 2
- Zone B
  - 9. Status 2
- Zone C
  - 10. Status 1A
  - 11. Status 1B
  - 12. Status 2
- Zone D
  - 13. Status 1A
  - 14. Status 1B
  - 15. Status 2
- Zone E
  - 16. Status 1A
  - 17. Status 1B
  - 18. Status 2

Modification = reduced WL deaths for Status 1A and 1B pts
Lung Allocation

• In May 2005, policy for lung allocation modified from allocation primarily by waitlist time to allocation based on the Lung Allocation Score (LAS)

• Previously those who were likely to survive long enough to receive a lung graft were frequently those who had the least anticipated benefit
  – Overall benefit of lung transplantation ~ 0

• LAS is calculated from estimates of waiting list survival probability AND expected post transplant survival probability (urgency and benefit)
  – In lung avoids futile transplants (unlike LIVER)

• Shift away from COPD -> IPF

• Listing practices have changed: older, sicker, previously transplanted, healthier patients listed much less frequently

• 1-year patient survival unchanged (=greater benefit?)
Components of Lung Allocation Score

Waitlist Urgency Measure
Shaded area under curve = Expected number of days lived without a transplant during an additional year on the waitlist

Post-Transplant Survival Measure
Shaded area under curve = Expected number of days lived during the first year post-transplant

<table>
<thead>
<tr>
<th>Factors used to predict waiting list survival</th>
<th>Factors used to predict posttransplant survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (% predicted)</td>
<td>FVC (% predicted)</td>
</tr>
<tr>
<td>PA systolic pressure</td>
<td>PCW mean pressure ≥ 20 mmHg</td>
</tr>
<tr>
<td>O₂ required at rest (L/min)</td>
<td>Continuous mechanical ventilation</td>
</tr>
<tr>
<td>Age at offer</td>
<td>Age at transplant</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>Serum creatinine (mg/dL)</td>
</tr>
<tr>
<td>NYHA functional status</td>
<td>NYHA functional status</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>Six-minute walk distance &lt;150 feet</td>
<td></td>
</tr>
<tr>
<td>Continuous mechanical ventilation</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
</tbody>
</table>

Source: SRTR.
Waitlist Survival vs. Transplant Benefit with Line Showing Suggested Allocation Balancing Urgency and Benefit

allocation by urgency and benefit

Transplant Benefit

Expected lifespan on waiting list

Transplant benefit threshold

SRTR

Table 4: Definitions and formulas to calculate Lung Allocation Score (LAS)

<table>
<thead>
<tr>
<th>LAS components</th>
<th>Definition or formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waiting list urgency measure</td>
<td>Expected number of days lived without a transplant during an additional year on the waiting list (area under the 1-year waiting list survival curve)</td>
</tr>
<tr>
<td>Posttransplant survival measure</td>
<td>Expected number of days lived during the first year following transplantation (area under the 1-year posttransplant survival curve)</td>
</tr>
<tr>
<td>Transplant benefit</td>
<td>Posttransplant survival measure – waiting list urgency measure, i.e. the number of expected additional days of life over the next year if a particular candidate received a transplant rather than remaining on the waiting list</td>
</tr>
<tr>
<td>Raw allocation score</td>
<td>Transplant benefit measure – waiting list urgency measure = (posttransplant survival measure – waiting list urgency measure) – waiting list urgency measure = posttransplant survival measure – 2 × (waiting list urgency measure)</td>
</tr>
<tr>
<td>Normalized lung allocation score</td>
<td>100 × (raw score + 2 × 365)/3 × 365</td>
</tr>
</tbody>
</table>

The possible range of values for the raw allocation score would be from +365 to −730 (the two extremes of 100% survival posttransplant but dying today without a transplant to a 100% chance of living for a year on the waiting list but a 100% probability of dying before the first day after a transplant). Because the Lung Allocation Subcommittee felt that negative allocation scores would be difficult to understand, it was decided to ‘normalize’ the score and produce a range from 0 to 100 according to the following formula: 100 × (raw score + 2 × 365)/3 × 365

Source: SRTR.
Summary

• There is no single best method of organ sharing
• Ethical/philosophical basis of allocation is organ-specific
  – Liver: Urgency = utility = benefit
  – Kidney: Equity ->-> mixed system
  – Pancreas: Equity -> more utilitarian elements
  – Heart: Mixed Equity/urgency
  – Lung: Mixed urgency/benefit
• Evolution of allocation policy tending to increase prioritization of urgency/benefit and reduction of geographic barriers