Liver Transplantation:
Past, Present and Future

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Chief of Hepatology
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Houston, Texas
In Memoriam
Thomas E. Starzl, M.D., Ph.D.
1926-2017

Pioneer in solid organ transplantation:
- Liver
- Kidney
- Multi-organ

Pioneer in immunosuppression:
- Cyclosporine
- Tacrolimus
- Micro-chimerism

Icon:
- Educator and mentor
- Advocate for patients and families
- Champion of hepatology
Past
**History of Transplantation**

- **1902**: First attempt at kidney transplant with human kidney
- **1936**: First attempt at kidney transplant
- **1954**: First successful kidney transplant
- **1963**: First liver transplant
- **1983**: First pediatric living donor liver transplant
- **1989**: Cyclosporine FDA approved
- **1994**: Tacrolimus FDA approved
- **1998**: First US adult living donor liver transplant
- **2002**: MELD implemented
# Initial Kidney Transplant Attempts:

<table>
<thead>
<tr>
<th>Year</th>
<th>Location</th>
<th>Surgeon</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1902</td>
<td>Lyon</td>
<td>Alex Carrel</td>
<td>Dog kidney tx into dog neck</td>
</tr>
<tr>
<td>1902</td>
<td>Vienna</td>
<td>Emerich Ulmann</td>
<td>Dog kidney tx into goat</td>
</tr>
<tr>
<td>1906</td>
<td>Lyon</td>
<td>Mathieu Jaboulay</td>
<td>Pig kidney tx into antecubital fossa</td>
</tr>
<tr>
<td>1909</td>
<td>Berlin</td>
<td>Ernest Unger</td>
<td>Monkey kidney tx into thigh</td>
</tr>
<tr>
<td>1936</td>
<td>Kherson</td>
<td>Yu Voronoy</td>
<td>First kidney tx using cadaveric human donor</td>
</tr>
<tr>
<td>1954</td>
<td>Boston</td>
<td>Joseph Murray</td>
<td>First successful kidney tx</td>
</tr>
<tr>
<td>1956</td>
<td>Boston</td>
<td>Joseph Murray</td>
<td>First tx using immunosuppression</td>
</tr>
</tbody>
</table>
Experimental Kidney Transplantation
First Successful Kidney Transplant
Experimental Liver Transplantation
First Liver Transplant

- March 1, 1963: First attempted human liver transplant
- July 23, 1967: First successful human liver transplant
First Attempts in Liver Transplantation: 1963-1964

<table>
<thead>
<tr>
<th>No.</th>
<th>Location</th>
<th>Age</th>
<th>Disease</th>
<th>Survival</th>
<th>Death</th>
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<tbody>
<tr>
<td>1</td>
<td>Denver</td>
<td>3</td>
<td>BA</td>
<td>0 days</td>
<td>hemorrhage</td>
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<tr>
<td>2</td>
<td>Denver</td>
<td>48</td>
<td>HCC</td>
<td>22 days</td>
<td>sepsis, PE</td>
</tr>
<tr>
<td>3</td>
<td>Denver</td>
<td>68</td>
<td>HCC</td>
<td>7 days</td>
<td>sepsis, PE</td>
</tr>
<tr>
<td>4</td>
<td>Denver</td>
<td>52</td>
<td>HCC</td>
<td>6 days</td>
<td>liver failure</td>
</tr>
<tr>
<td>5</td>
<td>Boston</td>
<td>58</td>
<td>Mets.</td>
<td>11 days</td>
<td>sepsis</td>
</tr>
<tr>
<td>6</td>
<td>Denver</td>
<td>29</td>
<td>HCC</td>
<td>23 days</td>
<td>sepsis</td>
</tr>
<tr>
<td>7</td>
<td>Paris</td>
<td>75</td>
<td>Mets.</td>
<td>0 days</td>
<td>hemorrhage</td>
</tr>
</tbody>
</table>
First Successful Multi-Organ Donor: 1968
Post-Moratorium Successes

- Anti-lymphocyte globulin (ALG) & the “triple cocktail”
- Improved organ preservation
- Codifying definition of “brain death”
Subsequent Progress

- **UCHSC (Denver) program, 1967-1983**
  - 1 year survival ~ 30%
  - ALG, Prednisone and Imuran

- **Introduction of cyclosporine, 1983**
  - 1-year survival increased to ~ 70%

- **Introduction of tacrolimus (Prograf), 1996**
  - 1-year survival ~ 85%
Milestones in Liver Transplantation

• 1968 Ad Hoc Committee of Harvard Medical School Published Criteria for Brain Death
• 1968 Uniform Anatomical Gift Act
• 1978 Uniform Brain Death Act
• 1983 NIH Consensus Development Conference:
  • “…Liver Transplantation is a therapeutic modality for end stage liver disease that deserves broader application.”
• 1984 National Organ Transplant Act:
  • Sale of organs prohibited
  • Development of UNOS
Deceased Donor Technique
Living Donor Liver
Recipient Technique for Liver Transplantation
Recipient Technique for Liver Transplantation
Modifications
Immunosuppression

Antigen-presenting cell → Helper T lymphocytes → Activated T lymphocytes

- Cyclosporin Tacrolimus
- Basiliximab Daclizumab

Antigen/T-cell receptor/MHC II → IL-2R

IL-2 → Sirolimus/RAD, Mycophenolate, Azathioprine → Proliferation
Improvements in Allograft Survival

Survival %

Time After Transplantation (years)

Before 1995

Kidney Transplant
Liver Transplant

After 1995

Kidney Transplant
Liver Transplant
Etiology of Liver Disease

- Hepatitis C
- ALD
- Other
- PBC/PSC
- Cryptogenic
- HCV/EtOH
- ALF
- Metabolic
- Other Viral
- Autoimmune
- ALD
- Hepatitis C
- PBC/PSC
- Other
- ALF
- Metabolic
- Other Viral
- Autoimmune
Indications for Liver Transplant

1. Life-threatening and progressive irreversible liver disease
2. Fulminant hepatic failure
3. Hepatopulmonary or hepatorenal syndrome
4. Worsening synthetic function
5. Ascites resistant to medical therapy
6. Hepatic encephalopathy
7. Variceal hemorrhage
8. Progressive malnutrition
9. Increasing fatigue that interferes with daily activities
10. Recurrent cholangitis
11. Development of hepatocellular carcinoma
Indication for Liver Transplantation

Evaluation Process
Hepatologist
Transplant Surgeon
Cardiologist
Nurse Coordinator
Social Worker
Laboratory Studies
Imaging (CT or MRI)

List for Transplant

Relative Contraindications
- Portal vein thrombosis
- Pulmonary hypertension
- Cholangiocarcinoma
- HIV

Absolute Contraindications
- Uncontrolled systemic infection
- Extra-hepatic malignancies
- Ongoing drug or alcohol use
- Inability to comply with post-transplant therapy

Medical Management
Present
Liver Allocation

- Status IA
- Status IB
- Local MELD/PELD
- Regional MELD/PELD: share 35
- National IA/IB
- National MELD/PELD
# MELD Score

<table>
<thead>
<tr>
<th>MELD</th>
<th>3 Month Mortality</th>
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<tr>
<td>&lt;10</td>
<td>2-8%</td>
</tr>
<tr>
<td>10-19</td>
<td>6-29%</td>
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<tr>
<td>20-29</td>
<td>50-76%</td>
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<tr>
<td>30-39</td>
<td>62-83%</td>
</tr>
<tr>
<td>&gt;40</td>
<td>100%</td>
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</table>
Disadvantages of MELD

- Uses only biochemical test results, including creatinine, which disadvantages females and is highly variable in cirrhotic patients.

- MELD Exception Points awarded for:
  - Ascites unresponsive to medical therapy
  - Hepatocellular Carcinoma
  - Recurrent Bacterial/Fungal Cholangitis
  - Hepatopulmonary Syndrome
  - Other conditions requiring Regional Approval
Live Donor OLT

Adult-to-Adult Live Donor

Adult-to-Child Live Donor
## MELD-Sodium

\[
\text{MELD} - \text{Na} - [0.025 \times \text{MELD} \times (140 - \text{Na})] + 140
\]

<table>
<thead>
<tr>
<th>MELD-Na⁺</th>
<th>3 Month Mortality</th>
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<tr>
<td>&gt; 40</td>
<td>71.3%</td>
</tr>
<tr>
<td>30–39</td>
<td>52.6%</td>
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<tr>
<td>20–29</td>
<td>19.6%</td>
</tr>
<tr>
<td>10–19</td>
<td>6.0%</td>
</tr>
<tr>
<td>&lt; 9</td>
<td>1.9%</td>
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MELD at Time of OLT in USA
Variance 2005-2015

Flavin CM: UNOS Policy Department, 2016
Current UNOS Regions

Flavin CM: UNOS Policy Department, 2016
Ratio of Eligible Deaths to Waitlisted Candidates with MELD $\geq$15
Proposed Revision of UNOS Regions: 2018

Flavin CM: UNOS Policy Department, 2016
SUPPLY : DEMAND

1:2
Adult 1-year posttransplant survival

Adult 1-year intent-to-treat survival from listing

Adult transplant rate

Original Investigation

Survival Benefit of Solid-Organ Transplant in the United States

Abbas Rana, MD; Angelika Gruessner, PhD; Vatche G. Agopian, MD; Zain Khalpey, MD, PhD; Irbaz B. Riaz, MBBS; Bruce Kaplan, MD; Karim J. Halazun, MD; Ronald W. Busuttil, MD, PhD; Rainer W. G. Gruessner, MD
<table>
<thead>
<tr>
<th>Transplant Type and Patient Category</th>
<th>No. of Patients</th>
<th>No. of Life-years</th>
<th>Observed No. of Life-years Saved to Date</th>
<th>Observed No. of Life-years Saved per Patient to Date</th>
<th>Median Survival, y</th>
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<tbody>
<tr>
<td>Kidney</td>
<td></td>
<td></td>
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<td>Waiting list</td>
<td>355 189</td>
<td>987 009</td>
<td>...</td>
<td>...</td>
<td>5.4</td>
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<tr>
<td>Transplant</td>
<td>314 561</td>
<td>2 246 383</td>
<td>1 372 959</td>
<td>4.4</td>
<td>12.4</td>
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<td>Liver</td>
<td></td>
<td></td>
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<td>Waiting list</td>
<td>134 826</td>
<td>218 026</td>
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<td>...</td>
<td>3.1</td>
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<tr>
<td>Transplant</td>
<td>112 319</td>
<td>659 637</td>
<td>465 296</td>
<td>4.3</td>
<td>11.6</td>
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<td>Heart</td>
<td></td>
<td></td>
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<tr>
<td>Waiting list</td>
<td>40 253</td>
<td>65 011</td>
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<td>358 555</td>
<td>269 715</td>
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<tr>
<td>Waiting list</td>
<td>24 688</td>
<td>43 564</td>
<td>...</td>
<td>...</td>
<td>2.3</td>
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<tr>
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<td>116 301</td>
<td>64 575</td>
<td>2.6</td>
<td>5.2</td>
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<td>Pancreas-kidney</td>
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<tr>
<td>Waiting list</td>
<td>14 195</td>
<td>33 979</td>
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<td>4.2</td>
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<tr>
<td>Transplant</td>
<td>16 995</td>
<td>119 620</td>
<td>79 198</td>
<td>4.6</td>
<td>14.5</td>
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<tr>
<td>Pancreas</td>
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<tr>
<td>Waiting list</td>
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<td>26 733</td>
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<td>8</td>
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<td>Transplant</td>
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<td>34 193</td>
<td>14 903</td>
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<td>13.3</td>
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<td>Intestine</td>
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<td>2086</td>
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<td>1.8</td>
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<tr>
<td>Transplant</td>
<td>1588</td>
<td>6256</td>
<td>4402</td>
<td>2.8</td>
<td>5.1</td>
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<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waiting list</td>
<td>579 506</td>
<td>1 376 408</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Transplant</td>
<td>533 329</td>
<td>3 540 945</td>
<td>2 270 859</td>
<td>4.3</td>
<td></td>
</tr>
</tbody>
</table>
What was accomplished?

Over 1 million LIFE YEARS
What was accomplished?

Over 400,000 LIFE YEARS
What was accomplished?

Over 250,000 LIFE YEARS
What efforts have we undertaken to increase the donor supply?

ONE OF THESE TWO WILL GET YOUR ORGANS. YOU DECIDE.
National adult liver donors vs. eligible donors and observed donation rate

The Donor Surge

National adult liver donors vs. death rate

- National crude death rate per 1,000 population
- National adult liver donors per million adult population

What is the Root Cause?

National adult liver donors by cause of death

3 year surge - total adult liver donors vs. anoxic adult liver donors

YEAR

STANDARDIZED ANOXIC ADULT LIVER DONORS

STANDARDIZED TOTAL ADULT LIVER DONORS


Anoxic adult liver donors per million adult population
National adult liver donors per million adult population

The Hypothesis

National standardized anoxic adult liver donors vs CDC drug overdose rate

UNOS Designation Drug Overdose

Per Million Population

Accounts for 30% of the SURGE

Linear regression analysis for change in CDC drug overdose rates vs. change in liver donors pmp by state

Association

Drug Abuse amongst Brain Dead Donors

- Social History: 11%
- Positive Tox Screen: 16%
- Positive Tox Screen and Social History: 20%
- No evidence of drug abuse: 47%

Ending the Opioid Epidemic — A Call to Action

Vivek H. Murthy, M.D., M.B.A.
New highs
United States, drug overdose deaths*, monthly

Source: Centres for Disease Control and Prevention

*Deaths involving more than one drug are counted multiple times
91 Americans die every day from an opioid overdose (that includes prescription opioids and heroin).
When did it start and when will it end?

Addiction Rare in Patients Treated with Narcotics

We need to plan ahead.

Yoeli D., et al. submitted for publication
Key Points

• Increasing the donor supply is the best strategy to improve intent-to-treat outcomes.
• 500,000 donors have provided over 2 million years of life.
• The Supply and Demand disparity is 1:2
• There is a recent surge in donors.
• The surge correlates with anoxic death donors.
• The surge is likely linked to the Opioid Epidemic
• We need to plan ahead and secure other sources of donors.
Reduction in Liver Transplant Wait-List in DAA Era

Cohort Study of 47,591 Adults in the UNOS Scientific Registry of Transplant Recipients Database 2003-2015

Annual Standardized Incidence Rates (ASIR) of LT Wait-Listing per 100,000 US Population

Listing rate for decompensated HCV cirrhosis decreased by 32% in the DAA era compared to the IFN era and is now equal to that of NASH

Indications for Wait Listing for OLT Non- HCC

Use of HCV Positive Donors

Increasing Proportion of HCV+ Recipients Receiving Younger HCV+ Donors

Percentage of HCV+ Recipients Receiving HCV+ Donors in U.S.

Median Donor Age by Recipients HCV Status

Bowring MG, AJT, 2017;17:519-527

Stewart, D., 2017 unpublished, based on OPTN data
While MELD scores improve in majority, there remains a risk of liver-related mortality for those with higher baseline MELD.

*Carrillo F, Hepatology 2017, Feb 7*
Treatment of Listed HCV Patients with Decompensated Cirrhosis

- HCV cure improves MELD in majority
  - Important if borderline function for LRT
  - Survival appears high if low baseline MELD
  - ~20% may avoid need for liver transplant

- Proportion (~30%+) will end up in MELD purgatory
  - May limit access to HCV+ donors
Can Modeling Help Decide Who Should be Treated?

Difference in life years if HCV is treated *pre-LT* versus *post-LT*

- Markov-based stimulation model compares survival in treating U.S. patients on the waiting list without HCC with MELD scores 10-40 with direct-acting antivirals (DAAs)
- Threshold for treating with DAAs *pre-LT* was MELD $\leq 27$

*Chhatwal J, Hepatology 2017;65:777-788*
Variations in Results by UNOS Regions:
UNOS Region 3: Shortest Waiting Time

Pre-LT Treatment Improves Life Expectancy if MELD ≤23

Chhatwal J, Hepatology 2017;65:777-788
HCV Treatment Pre- OR Post-LT?
UNOS Region 9: Long Waiting Time

Pre-LT Treatment Improves Life Expectancy if MELD ≤27

Chhatwal J, Hepatology 2017;65:777-788
HCV-Treatment of Wait-Listed Patients

- For liver transplant candidates, treatment needs to be careful consideration of:
  - Risk of dying in absence of treatment
  - Anticipated timeline for improvement in decompensation
  - Prioritization for LT and potential harm if some but not enough improvement

- Available data suggests those with MELD <20-27 points likely derive clinical benefit
  - Delisting and/or survival benefit
  - MELD cut-off strongly influenced by waiting time
  - Other factors of importance may be concurrent HCC (and need for LRT) and availability of HCV+ donors

- There is high need for high quality longitudinal studies of wait-listed patients and predictors of outcomes
Future
“Predictions are dangerous, especially ones about the future.”

Lorenzo Pietro “Yogi” Berra
Global Impact of Chronic Liver Diseases
Prevalence of Cirrhosis Per 100,000 Persons

Alcohol cause of 47.9% cirrhosis*

Unmet Need for Donor Organs
Major Options

- Increase Donor Supply
  - Change from Opt In to Opt Out policy
  - Increase live donation
  - Perfect xenografts
  - Develop bioengineered organs

- Change Allocation System
  - Change from sickest first to highest utility policy
  - Rational rationing
  - Revise UNOS Regions
Unmet Need for Donor Organs
Better Long-Term Option

Prevent
Chronic Liver Diseases
and Progression to Cirrhosis

- Addresses root causes
- Cost effective
- Greatest long-term benefits
- Requires Societal and Pharma commitment to translational research and development of new therapies and diagnostics
Translational Medicine: Need for Greater Bidirectional Balance and More Academic-Industry Partnerships

Oversold Promises $1.4 billion/NDA

Under Appreciated Promise to Define Pathogenic Mechanisms*
Personalized Therapies

*Brenner, S, 2012
Can We Aspire to a World Without Liver Diseases?

You see things and you say, “Why?”
But I dream things that never were and say, “Why not?”

George Bernard Shaw
Thank You!

Texas Medical Center

New Research Park and Hospital