Changing the Rules in Transplantation: Separating Science from Stigma

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Chief, Division of Transplantation
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Breaking news: **Feb. 4, 2020** – “The Organ Procurement and Transplantation Network (OPTN) has implemented a new liver and intestinal organ distribution system to improve the process of matching life-saving organs to candidates in greatest need of them.”

“New system replaces decades old geographic boundaries of 58 DSAs and 11 regions…” Livers from all deceased donors will first be offered to the most urgent liver transplant candidates (Status 1A and 1B) listed at transplant hospitals within a radius of 500 nautical miles of the donor hospital. Following offers to the most urgent candidates, livers from adult donors will be offered to candidates at hospitals within distances of 150, 250 and 500 nautical miles of the donor hospital.”

(pending UNOS Board Approval) Under the newly approved kidney system, expected to be implemented in 2020, kidney and pancreas offers (except for rare, very well-matched donor and recipient combinations nationwide) will be offered first to candidates listed at transplant hospitals within 250 nautical miles of the donor hospital. Offers not accepted for any of these candidates will then be made for candidates beyond the 250 nautical mile distance.
58 OPO Donation Service Areas in the U.S.

OPO Data
Population Bases from 1.2 Million to 18.9 Million
Deceased Donors Recovered ranged from 32 to 439 Donors
Donors per million (dpm) ranged from 17 to 44 DPM: 26.5 mean
New Liver Allocation Maps - 150 nautical miles (172.6 miles)
New Liver Allocation Maps - 250 nautical miles (287.7 miles)
New Liver Allocation Maps - 500 nautical miles (575.4 miles)
New Rules-allocation

- moving away from historical precedent
- to data driven policy: statistical modeling projects it will save lives (less waitlist deaths)
- more fair: provides more equitable access based on need

Concern but good policy…

3 more examples:
- liver transplantation and the six-month rule
- Hep C positive donors into negative reciprs
- utilizing HIV positive donors
**Who to transplant:** Case: Severe Alcoholic Hepatitis

- 61 yo female, school teacher, admitted to Northern Maine medical center with SAH.
  - Heavy alcohol use, but didn’t interfere with work, no DUIs or negative consequences
  - Failed steroids, Transferred to hospice
- PCP advocated and found Hopkins publication, initiated transfer to JHH for work-up
- Excellent social support, husband at bedside - Transplant?
UNOS Board, November 1996

Exclusionary Criteria

1. In the patient with alcoholic liver disease, the presence of acute alcoholic hepatitis is an absolute contraindication to liver transplantation. Transplantation of these patients has resulted in poor survival rates. In addition, these patients have demonstrated unacceptably high recidivism rates. This makes them extremely high-risk patients for transplant, both from a medical standpoint and from a psycho-social standpoint. Therefore, these patients are excluded from consideration as liver transplant recipients.

2. All patients who have a history of alcoholism must demonstrate at least a six-month period of abstinence prior to being considered as candidates for liver transplantation. Those patients who, at the time of their presentation to the transplant center, have a period of abstinence documented to be longer than six months must still be evaluated by a health care professional with extensive experience in the care and treatment of patients with a history of substance abuse.
UNOS Board, November 1996

Dr. Burdick then adjourned the meeting to the Executive Session.

The open session resumed, and Andrew S. Klein, M.D., Chairman of the Liver and Intestinal Organ Transplantation Committee, introduced several resolutions from that Committee dealing with modifications to the Liver Allocation Policies.

The Board then adopted, by a vote of 27 for; 8 against; and 0 abstentions, the recommendation of the Minority Affairs Committee to amend the standard minimum listing criteria for Liver Transplantation as follows:

RESOLVED, that the following criteria proposed by the Liver and Intestinal Organ Transplantation Committee under Section 1, Alcoholic Cirrhosis, B, Exclusionary Criteria, 2 and 3, of the Proposed LINOS Standard Minimum Patient Listing Criteria for Liver Transplantation, shall be amended as set forth below:

All patients who have a history of alcoholism must demonstrate at least a six-month period of abstinence prior to being considered as candidates for liver transplantation. All those patients with a history of alcoholism who, at the time of their presentation to the transplant center, have a period of abstinence documented to be longer than six-months must still be evaluated by a health care professional with extensive experience in the care and treatment of patients with a history of substance abuse. This may be a psychiatrist, psychologist, social worker, substance abuse counselor, or other individuals with this expertise. If these alcoholic patients are deemed an acceptable risk by the substance abuse professional, they do not need to undergo the written contract described in Section 3. The findings of the health care professional must be documented and be available for review.

Those patients who have not demonstrated at least six months of sobriety must complete an evaluation by the substance abuse professional as described above, and, in addition, must enter into a written contract or agreement with the substance abuse professional and the transplant team.
Early Liver Transplantation for Severe Alcoholic Hepatitis

Philippe Mathurin, M.D., Ph.D., Christophe Moreau, M.D., Ph.D., Didier Samuel, M.D., Ph.D., Jérôme Dumortier, M.D., Ph.D., Julia Salleron, M.S., François Durand, M.D., Ph.D., Hélène Castel, M.D., Alain Duhemel, M.D., Ph.D., Georges-Philippe Pagesu, M.D., Ph.D., Vincent Leroy, M.D., Ph.D., Sébastien Darancy, M.D., Ph.D., Alexandre Louvet, M.D., Ph.D., Emmanuel Bledel Isard, M.D., Ph.D., Valérie Lucidi, M.D., Thierry Gustot, M.D., Ph.D., Jacques Belghiti, M.D., Vincent Donckier, M.D., Ph.D., François-René Pruzen, M.D., and Jean-Charles Duchossois-Vallée, M.D., Ph.D.

ABSTRACT

BACKGROUND

A 6-month abstinence from alcohol is usually required before patients with severe alcoholic hepatitis are considered for liver transplantation. Patients whose hepatitis is not responding to medical therapy have a 6-month survival rate of approximately 30%. Since most alcoholic hepatitis deaths occur within 2 months, early liver transplantation is attractive but controversial.

METHODS

We selected patients from seven centers for early liver transplantation. The patients had no prior episodes of alcoholic hepatitis and had scores of 0.6 or higher according to the MELD model (which calculates scores ranging from 0 to 40, with a score of 25 indicating nonresponse to medical therapy and an increased risk of death in the absence of transplantation) or rapid worsening of liver function despite medical therapy. Selected patients also had supportive family members, no severe coexisting conditions, and a commitment to alcohol abstinence. Survival was compared between patients who underwent early transplantation and matched patients who did not.

RESULTS

In all, 26 patients with severe alcoholic hepatitis in high risk of death (median MELD score, 30) were selected and placed on the list for a liver transplant within a median of 13 days after nonresponse to medical therapy. Fewer than 2% of patients admitted for an episode of severe alcoholic hepatitis were selected. The criteria used 30% of available grafts for this indication. The cumulative 6-month survival rate was higher among patients who received early transplantation than among those who did not (77% vs. 28%, P=0.001). This benefit of early transplantation was maintained through 5 years of follow-up (hazard ratio, 6.58; 95% CI, 1.60 to 26.0). These patients were drinking alcohol at 720 days, 1 at 740 days, and 1 at 1140 days after transplantation.

CONCLUSIONS

Early liver transplantation can improve survival in patients with a first episode of severe alcoholic hepatitis not responding to medical therapy. (Funded by Société Française de Gastroentérologie.)

Figure 1. Kaplan-Meier Estimates of Survival in the 26 Study Patients and the 26 Best-Fit Matched Controls.

-26 patients with AH
-77% 6m survival
-12% recidivism
Patients required all of the following to be selected for our pilot program:

1) Severe alcoholic hepatitis (Discriminant Function ≥ 32) as first liver-decompensation (i.e. patient not aware of liver disease prior).
2) Failure of medical management, guided by Lille Score > 0.45, continuous increase in MELD, or consensus by fellow, transplant surgeon, and medical hepatologist.
3) Commitment to lifelong adherence to alcohol abstinence, evaluated by substance abuse specialist, with rigorous assessment and classification of alcohol history and dependency.
4) Strong social support by family and friends, evaluated by transplant social worker.
5) Rigorous assessment of possible risk factors for alcohol relapse, by substance abuse specialist and social worker.
6) Absence of severe comorbid medical issues, evaluated by hepatologists, transplant surgeon, and other medical specialists when appropriate.
7) If history of psychiatric disease, evaluated by transplant psychologist, with required assessment of stable psychiatric disease.
8) Full consensus agreement by transplant committee, comprised of social worker, hepatologist, transplant surgeon.
LT for AH at JHU

• Recipient characteristics
  (5 yr follow up)

• Group 1: AH (n=46)

• Group 2: >6m sober
  (n=34)
LT for AH at JHU

- **Results**
  - 6m survival: 98%
  - 1yr survival: 98%
  - Recidivism: 28%

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Chronic cirrhotic (N = 34)</th>
<th>SAH (N = 46)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up time, days, median (IQR)</td>
<td>678 (371, 1120)</td>
<td>484 (262, 935)</td>
<td>0.20*</td>
</tr>
<tr>
<td>One year patient survival (N = 27, 30)</td>
<td>27 (100%)</td>
<td>29 (97%)</td>
<td>1.00</td>
</tr>
<tr>
<td>One-year graft survival</td>
<td>24 (89%)</td>
<td>28 (93%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Six month patient survival (N = 31, 41)</td>
<td>31 (100%)</td>
<td>40 (98%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Six month graft survival</td>
<td>29 (94%)</td>
<td>33 (95%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Any alcohol relapse</td>
<td>8 (24%)</td>
<td>13 (28%)</td>
<td>0.80</td>
</tr>
<tr>
<td>Alcohol relapse with harmful patterns*</td>
<td>4 (13%)</td>
<td>8 (17%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Death-censored sobriety at follow-up (N = 31, 41)</td>
<td>30 (97%)</td>
<td>39 (95%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Post-transplant infection</td>
<td>19 (56%)</td>
<td>24 (52%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Post-transplant malignancy</td>
<td>2 (6%)</td>
<td>4 (9%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Any episode of rejection post-transplant</td>
<td>15 (44%)</td>
<td>18 (39%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Study:</td>
<td>NEJM (France)</td>
<td>AJT (Mt. Sinai)</td>
<td>JHU</td>
</tr>
<tr>
<td>-----------------</td>
<td>---------------</td>
<td>-----------------</td>
<td>------</td>
</tr>
<tr>
<td>n</td>
<td>26</td>
<td>9</td>
<td>46</td>
</tr>
<tr>
<td>Survival (6m)</td>
<td>77%</td>
<td>89%</td>
<td>98%</td>
</tr>
<tr>
<td>Recidivism</td>
<td>12%</td>
<td>11%</td>
<td>28%</td>
</tr>
</tbody>
</table>
Case: Severe Alcoholic Hepatitis

• Transplanted, d/c’d POD 12
• No recidivism
• Now retired - volunteering for church
Multidisciplinary Approach to Study of Patients with Severe Alcoholic Hepatitis Undergoing Liver Transplantation
Center Research Plan
Project 1: Cohort/Ethics study

Figure 5. Retrospective and Prospective Clinical Cohorts

Retrospective Cohort

ELT for SAH pts
N=50

Prospective Cohort

ELT for SAH pts
N=100

ALD OLT pts
N=100

Evaluation and Transplantation

Post-Transplant Care and Medical and Behavioral follow-up
Center Research Plan

- Characterize the Johns Hopkins cohort undergoing ELT at both a macro and micro level via the following four highly interactive and interdependent projects:

  - **Project 1:** “Cohort/Ethics study of Patients with SAH undergoing ELT” (Cameron)

  - **Project 2:** “Optimization of Post-transplant care via Biomarkers and Behavioral interventions” (McCaul/Chander)

  - **Project 3:** “Proteomic analysis of explanted livers with characterization of autoantigens” (Zhu)

  - **Project 4:** “Animal transplant models to characterize immune and regenerative effects of alcohol” (Sun)
Conclusions: ELT for SAH at JHU

- Life Saving therapy for patients with no other option
- Outcomes similar to patients with ongoing sobriety (95%)
- Need for biologic investigation is just as great (NIAAA P50)
- Calls into question the value of the 6 month wait rule
Now, **How to get them transplanted:**

- HIV
- HCV
Consider... HIV

Treatment with HIV medicines can prevent HIV from developing into AIDS

3/19/16: HIV to HIV LT
Clinical Transplantation

ORIGINAL ARTICLE  Full Access

HIV+ deceased donor referrals: A national survey of organ procurement organizations

Ayla Cash, Xun Luo, ... See all authors

First published: 09 December 2017  https://doi.org/10.1111/ctr.13171  Cited by: 1

Funding information National Institutes of Health: K23CA177321-01A1 (Durand), R34AI123023 (Durand), 1R01AI120938-01A1 (Tobian), K24DK101828 (Segev), F30DK116658-01 (Shaffer), Johns Hopkins University Center for AIDS Research: 1P30AI094189 (Durand).

Read the full text

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Moving from the HIV Organ Policy Equity Act to HIV Organ Policy Equity in action: changing practice and challenging stigma

Brianna L. Doby; Aaron A.R. Tobian; Dorry L. Segev; Christine M. Durand
Hope act results (JHU)

<table>
<thead>
<tr>
<th>Pt</th>
<th>Demo</th>
<th>Dx (HIV)</th>
<th>MELD</th>
<th>Donor</th>
<th>Donor Age</th>
<th>Surv</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 YB</td>
<td>49y AA F</td>
<td>HCV</td>
<td>8</td>
<td>CT</td>
<td>35</td>
<td>1.5y</td>
</tr>
<tr>
<td>2 GL</td>
<td>67y W M</td>
<td>NRH</td>
<td>13</td>
<td>IL</td>
<td>25</td>
<td>1.5y</td>
</tr>
<tr>
<td>3 KT</td>
<td>46 y AA M</td>
<td>HCV/HCC</td>
<td>7</td>
<td>DC</td>
<td>44</td>
<td>1y</td>
</tr>
<tr>
<td>4 EW</td>
<td>52 y AA M</td>
<td>HCV</td>
<td>39</td>
<td>NY</td>
<td>70</td>
<td>10m-</td>
</tr>
<tr>
<td>5 AS</td>
<td>62y AA M</td>
<td>HCV</td>
<td>8</td>
<td>TX</td>
<td>46</td>
<td>6m-</td>
</tr>
<tr>
<td>6 RB</td>
<td>66y WM</td>
<td>HBV</td>
<td>8</td>
<td>AL</td>
<td>41</td>
<td>6m-</td>
</tr>
<tr>
<td>7 MM</td>
<td>55y AA M</td>
<td>HCV</td>
<td>22</td>
<td>NJ</td>
<td>19</td>
<td>4m-</td>
</tr>
<tr>
<td>8 JD</td>
<td>56y W M</td>
<td>NASH</td>
<td>18</td>
<td>GA</td>
<td>52</td>
<td>3m-</td>
</tr>
<tr>
<td>9 RA</td>
<td>67y AA F</td>
<td>HCV/HCC</td>
<td>6</td>
<td>NY</td>
<td>27</td>
<td>2m-</td>
</tr>
<tr>
<td>10 ET</td>
<td>54y W F</td>
<td>HCV</td>
<td>17</td>
<td>FL</td>
<td>56</td>
<td>1m-</td>
</tr>
</tbody>
</table>
Consider HCV: miracle drugs and the OD epidemic

<table>
<thead>
<tr>
<th></th>
<th>Hep A</th>
<th>Hep B</th>
<th>Hep C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Virus</strong></td>
<td>Picornavirus (RNA)</td>
<td>Hepadnavirus (DNA)</td>
<td>Flavivirus (RNA)</td>
</tr>
<tr>
<td><strong>Transmission</strong></td>
<td>Fecal-oral (food, personal contact)</td>
<td>Parenteral (perinatal, IVDA, sexual)</td>
<td>Parenteral (IVDA, Blood products pre 1990)</td>
</tr>
<tr>
<td><strong>Acute disease?</strong></td>
<td>Common</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Evolution to chronic disease?</strong></td>
<td>Never</td>
<td>Infrequent in adults</td>
<td>Frequent (70%)</td>
</tr>
<tr>
<td><strong>New cases/year</strong></td>
<td>180,000</td>
<td>180,000</td>
<td>40,000</td>
</tr>
<tr>
<td><strong># Infected (US)</strong></td>
<td>-</td>
<td>1,250,000</td>
<td>4,000,000</td>
</tr>
<tr>
<td><strong>Worldwide</strong></td>
<td>-</td>
<td>350,000,000</td>
<td>170,000,000</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>None</td>
<td>Lamivudine Adefovir</td>
<td>Interferon +Ribavirin</td>
</tr>
<tr>
<td><strong>Prophylaxis</strong></td>
<td>Recombinant vaccine and Immune globulin</td>
<td>Recombinant vaccine and immune globulin</td>
<td>None</td>
</tr>
</tbody>
</table>
## Prices Climb

The cost of drugs is rising, especially for rare disorders.

A selection of some of the most expensive drugs, annual cost in the U.S.

<table>
<thead>
<tr>
<th>Drug (company)</th>
<th>Treats</th>
<th>Typical/Annual Cost</th>
<th>Target patient population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soliris (Alexion)</td>
<td>Type of blood disease and also a kidney disorder</td>
<td>$440,000</td>
<td>10,000-12,000 world-wide</td>
</tr>
<tr>
<td>Natirxzyme (Genentech)</td>
<td>Rare enzyme disorder</td>
<td>$400,000</td>
<td>1,100 in developed countries</td>
</tr>
<tr>
<td>Elaprase (Shire/Sanoft)</td>
<td>Rare enzyme disorder</td>
<td>$375,000</td>
<td>2,000 world-wide</td>
</tr>
<tr>
<td>Cinryze (Shire)</td>
<td>Hereditary Angioedema</td>
<td>$350,000</td>
<td>6,000 in U.S.</td>
</tr>
<tr>
<td>Gattex (NPS)</td>
<td>Short Bowel Syndrome</td>
<td>$295,000</td>
<td>3,000-5,000 in U.S.</td>
</tr>
<tr>
<td>Harvoni (Gilead)</td>
<td>Hepatitis C</td>
<td>$94,500</td>
<td>3.2 million in U.S.</td>
</tr>
</tbody>
</table>

Source: Sector & Sovereign Research (price changes); Needham & Co. (drugs, patient population); Centers for Disease Control and Prevention (patient population)

**JHU waitlist: 500 pts**

**2016: HCV pos: 40%**

**Now: 8**
The Drug Overdose Epidemic and Deceased-Donor Transplantation in the United States: A National Registry Study

Christine M. Durand, MD *; Mary G. Bowring, MPH *; Alvin G. Thomas, MSPH; Lauren M. Kucirka, MD, PhD; Allan B. Massie, PhD; Andrew Cameron, MD, PhD; Niraj M. Desai, MD; Mark Sulkowski, MD; Dorry L. Segev, MD, PhD
# HCV pos donor into negative recip results (JHU)

<table>
<thead>
<tr>
<th>Pt</th>
<th>Demo</th>
<th>Dx</th>
<th>HCV RNA d3</th>
<th>Tx</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 FK</td>
<td>21y AA F</td>
<td>ALF</td>
<td>NA</td>
<td>NA</td>
<td>Exp POD3</td>
</tr>
<tr>
<td>2 MS</td>
<td>24y WM</td>
<td>BA (redo)</td>
<td>25,000,000</td>
<td>Harvoni</td>
<td>SVR</td>
</tr>
<tr>
<td>3 NM</td>
<td>21y WM</td>
<td>PSC</td>
<td>287,000</td>
<td>Harvoni</td>
<td>SVR</td>
</tr>
<tr>
<td>4 TC</td>
<td>53y WM</td>
<td>ETOH</td>
<td>34,000,000</td>
<td>Mavyret</td>
<td>SVR</td>
</tr>
<tr>
<td>5 JB</td>
<td>60y WM</td>
<td>PVT</td>
<td>1,160,000</td>
<td>Mavyret</td>
<td>On tx</td>
</tr>
<tr>
<td>6 MT</td>
<td>59y WM</td>
<td>NASH</td>
<td>22,600,000</td>
<td>Mavyret</td>
<td>On tx</td>
</tr>
<tr>
<td>7 JS</td>
<td>66y WM</td>
<td>NASH</td>
<td>29,800,000</td>
<td>Mavyret</td>
<td>On tx</td>
</tr>
<tr>
<td>8 NC</td>
<td>53y WM</td>
<td>ETOH</td>
<td>52,300,000</td>
<td>Mavyret</td>
<td>On tx</td>
</tr>
</tbody>
</table>
Conclusions

-new policies: based on data/science, not tradition/stigma

- allocation
- who gets transplanted
- what donors we can use...
The team
The grants

NIH (active Grants-JHU Div of Transplant):

R01DK096008  K01AG043501  F30DK09554  U01AI134591
R01DK098431  K01DK101677  F32DK105600  U01AI38897
R01AG042504  K08DK092287  F32AG044994  P50AA027054
R01DK111233  K08HS023876  F32AG053025
R01DK111966  K23DK115908  F32DK113719
R01AI120938  K24DK101828
R01AG055781
R01DK114074
The patients