Liver Transplantation for Alcohol-related Hepatitis

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- Rescue liver transplantation, when used as a treatment for severe alcoholic hepatitis, is life-saving;
- Is becoming more widespread in Europe and the USA...

Why is it not standard of care?
Why is rescue LT not standard of care for life-threatening AH?

Outcome
• Confusion about the endpoint
• No consensus to accept data on efficacy

Process
• Difficulties predicting patient prognosis
• Inconsistency in patient selection

Social viability
• Dynamics of transplantation
• Impact on stakeholders

Endpoint Determination? or
Early Liver Transplantation for Severe Alcoholic Hepatitis

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Figure 1: Kaplan–Meier Estimates of Survival in the 26 Study Patients and the 26 Best-Fit Matched Controls.
Rescue LT for AH in the US: a 2017 Snapshot  
*Lee B et al, AASLD 2017*

- Retrospective data from 12 U.S. centers
- Consecutive LT recipients; severe AH, no prior liver disease
- 147 patients:
  - median duration of abstinence pre-LT: 55 days (range: 36-91)
  - 54% received C’steroids
  - MELD at LT: 39 (range: 35-40).
- Post-LT survival: 94% and 84% at 1 and 3 years (med follow-up: 18 mo)
- 9/18 deaths occurred within 3 months of LT: 8 had received C’steroids, 5 of whom died of sepsis. The other 9 deaths occurred >1-year post-LT; 7 alcohol-related.
- Drinking history: 141 survivors:
  - Abstinent: 101 (72%)
  - Slips: 25 (18%)
  - Sustained use: 15 (11%)

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Trajectories of Alcohol Use after Liver Transplantation for Alcoholic Cirrhosis  
*DiMartini A et al, Am J Transpl 2010*

<table>
<thead>
<tr>
<th>Pattern of use</th>
<th>% cohort</th>
</tr>
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<tbody>
<tr>
<td>None</td>
<td>51.3%</td>
</tr>
<tr>
<td>Occasional, low level</td>
<td>28.6%</td>
</tr>
<tr>
<td>Early onset, accelerates and declines</td>
<td>6.4%</td>
</tr>
<tr>
<td>Delayed increase to moderate use</td>
<td>7.9%</td>
</tr>
<tr>
<td>Early onset, increasing heavy use</td>
<td>5.8%</td>
</tr>
</tbody>
</table>
Consequences of Alcohol Relapse after Liver Transplantation

- More frequent medical problems: pneumonia, pancreatitis, delerium tremens, depression
- Marital breakdown, drunk driving, work absences
- Graft loss due to ALD is rare in the first 5 years, but may occur at 10 years in heavy drinkers
Meta Analysis of Individual Data from 4 RCTs of Corticosteroids in Patients with Severe Alcoholic Hepatitis. *Mathurin et al. GUT 2010*

### Predicting Patient Prognosis

- **Clinical diagnosis** of alcoholic hepatitis
- **Maddrey DF** = 32.
- **Exclusions:** renal failure (defined as a creatinine level >500 μmol per liter [>5.7 mg per deciliter], or renal-replacement therapy), active GI bleeding, untreated sepsis, or requiring inotropic support
- **Mean interval to treatment:** 6 days
- **Predicted 28-day mortality** in the double placebo (ie natural history) group was 30%

<table>
<thead>
<tr>
<th>STOPAH Mortality at 28 Days</th>
<th>Treatment Group</th>
<th>Patients (n = 1103)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pred/ pentoxi</td>
<td>274</td>
<td>13.5</td>
<td></td>
</tr>
<tr>
<td>Pred/ placebo</td>
<td>277</td>
<td>14.3</td>
<td></td>
</tr>
<tr>
<td>Pentoxi/ placebo</td>
<td>276</td>
<td>19.4</td>
<td></td>
</tr>
<tr>
<td>Double placebo</td>
<td>276</td>
<td>16.7</td>
<td></td>
</tr>
</tbody>
</table>
How important is Alcohol-relapse as a Determinant of Suitability for LT?

A paradox:

• Recent studies of patients who survive an episode of severe AH( Louvet A et al, Altamirano et al) have shown that alcohol relapse is the main driver of long-term mortality.

• As shown in the US retrospective LT cohort, ~ 5% of patients die an alcohol-related in the first 2 years post-LT

• After LT in ALD without AH, the impact of alcohol relapse is related to sustained drinking usually takes 5-10 years to impact allograft function or impact survival.
In a 2015 pilot survey, we received responses from 42 of 134 US LT Centers (comprising 50% of all transplants in 2014)

What interval of abstinence does your center require?

- 6 months: 24
- 3 months: 2
- 1 month: 1
- Situational dependent: 2
- Not required: 1
- Unsure: 15

Decision making in liver transplant selection committees: a multicenter study.

- Prospective evaluation of 4 US transplant selection committees
- The authors found:
  - Absent written program rules regarding addictions
  - Inconsistent judgments within committees
  - Lack of consensus between committee members
  - Expression of opinions outside committee member’s areas of expertise
- Alcohol-use disorder patients posed the most difficult dilemmas
Selection of AH patients for LT: le modèle français

Clinical Liver Disease
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Transplant Evaluation for ALD
January 1, 2012 – December 31, 2014
232 Patients

< 6 Months Sobriety
116 Patients

Not Selected
43 Patients
Selected
73 Patients

> 6 Months Sobriety
116 Patients

Not Approved
46 Patients
Approved
70 Patients

Multidisciplinary Psychosocial Liver Transplant Evaluation in Patients with Alcohol-related Liver Disease – An Alternative To The ‘Six-month Rule’

The University of Wisconsin Experience
Dynamics of Transplantation

Organ Availability

Definition of Success

Patient Need

Dynamics of Transplantation

For ALD

Organ Availability

Public support for donation

The relationship With addiction

Definition of Success

Personal Responsibility

Patient Need
Good Afternoon Dr. Lucey-
I am responding today about the Prior Authorization for Mr. YYY. As you pointed out, the certificate language at XXX for alcoholic cirrhosis and liver transplant states that a member must be abstinent of alcohol for 12 months to qualify for coverage. This does appear to be an outlier in terms of duration... Therefore, my team and I looked at several other certificates and medical policies from other insurers as well as referencing 3rd party sources of information... for guidelines for medical necessity.
1. Blue Cross/Blue Shield’s certificate states liver transplants are not covered in patients with ongoing alcohol and/or drug abuse. (Evidence for abstinence may vary among liver transplant programs, but generally a minimum of 3 months is required.)
2. Aetna’s certificate does not cover for “active alcoholism” and requires a “period of abstinence” the length of which they don’t describe on their public documents
3. Dean’s certificate requires 6 months of abstinence
4. PPPlus’ certificate requires 6 months of abstinence
5. Unity’s certificate does not get into the specific criteria of any organ transplant
6. Cigna’s certificate does not cover in “ongoing alcohol abuse”
7. MCG, which is our main source of evidence-based, independent medical criteria, has a 6 month wait to meet criteria.
8. Liver Foundation’s website states that for liver transplant, “For transplant to be an option, you’d need to find a transplant center that would consider you and then meet the requirements of the program, including abstaining from alcohol for six months prior to transplant and agreeing not to resume drinking afterward.”
9. UpToDate states “For patients with alcoholic liver disease, most programs require a minimum period of abstinence of at least six months, participation in a structured rehabilitation and abstinence program, and adequate social support to help maintain sobriety”...
While I concede that 12 months on XXX’s certificate is too long, even if I waive the certificate language and look to MCG, a 6 month period of abstinence would still be required. Looking at the other criteria listed above, 6 months certainly seems to be a reasonable standard. For that reason, I will uphold the denial for Mr. YYY with the caveat that if he can demonstrate 6 months of sobriety from alcohol and other substances abuse, that we would approve him, assuming that he passed the remainder of the medical necessity criteria at that time.
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"Dove c’è una grande volontà, non possono esserci grandi difficoltà".
Where the willingness is great, there can not be great difficulties.