Early Liver Transplantation in Severe Alcoholic Hepatitis: How will it look like in 2018?

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Moving toward the Response
Guided therapy
Lille model: a tool for new strategies
Evaluation of Lille model on overall patients (n=438)

http://www.lillemodel.com

Lille score < 0.45: 85±2.5%
Lille score ≥ 0.45: 25±3.8%

p<0.00001

Louvet A et al, Hepatology 2007
Alcohol consumption is not restricted to patients transplanted for ald.
Alcohol use post liver transplantation
ALD versus non-ALD

Abstinence < 6 months OR: 7.8; 95 % CI: 4-15.3; p<0.05

Bravata DM, Liver Transpl 2001
The 6-Month Rule: Where are the data?
Background
The 6-month: a questionable criterion in the setting of severe alcoholic hepatitis

• The 6-month period of abstinence is presumed:
  - a) to identify subsets of patients likely to maintain abstinence after liver transplantation.
  - b) to permit some patients to recover from their liver disease and obviate the need for liver transplantation.
6month rule: where are the data?

Liver transplantation for alcoholic liver disease: bias, beliefs, 6-month rule, and relapse— but where are the data.

Foster PF, Hepatology 1997

Beresford TP, Everson GT, Liver Transpl 2000
6month rule: where are the data?

Bad exclusion criterion

Good inclusion criterion

58.6%

Foster PF, Hepatology 1997
6-month Abstinence: Is it Justified by the Evidence?

- Allen vs. Mansour case, Michigan court in 1986
- Medicaid 2-year abstinence requirement for LT
- “Arbitrary and unreasonable”
  - High operative risks
  - May not survive the waiting period

- **WITHOUT** enough 6-month evidence, expert opinions

Consensus Conference: Indications for Liver Transplantation, January 19 and 20, 2005, Lyon-Palais Des Congrès

Text of Recommendations (Long Version)

The Jury stated:
- wait-and-watch strategy using the 6-month criterion may be unfair for some non-responders with 70-80% probability of dying during this period
- recommended pilot studies evaluating early liver transplantation in non-responders
Early Liver Transplantation for Severe Alcoholic Hepatitis

Philippe Mathurin, M.D., Ph.D., Christophe Moreno, 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 Duhamel, M.D., Ph.D., Georges-Philippe Pageaux, M.D., Ph.D., Vincent Leroy, M.D., Ph.D., Sébastien Dharancy, M.D., Ph.D., Alexandre Louvet, M.D., Ph.D., Emmanuel Boleslawski, M.D., Ph.D., Valerio Lucidi, M.D., Thierry Gustot, M.D., Ph.D., Claire Francoz, M.D., Christian Letoubon, M.D., Denis Castaing, M.D., Jacques Belghiti, M.D., Vincent Donckier, M.D., Ph.D., François-René Pruvot, M.D., and Jean-Charles Duclos-Vallée, M.D., Ph.D.
Early LT in Alcoholic hepatitis

Methods

• Early liver transplantation in non-responders undergoing their first event of liver disease

• Non responders were identified using Lille score $\geq 0.45$ or worsening of liver function by day 7.

• Patients were drastically selected using those criteria:
  - absolute consensus of paramedical and medical staff
  - no co-morbidities
  - social integration
  - supportive family members
  - psychiatric evaluation and addictive profile

Intervention of 4 decision circles:

- **Algorithm (1)**

  - Family circle
    - Patient

- **Nurses, house physician, assistants and clinic director**
- **Addiction specialist**
- **Séniors anesthesiologists and surgeons**

Early LT in Alcoholic hepatitis

* Maximum of Lille score is 1

Early LT in Alcoholic hepatitis

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

Early Transplantation shift survival of unresponsive to responders

• Final combined database included a total of 651 patients. Matching was performed using the global optimal algorithm.

• For matching criteria, we used the following pre-established ranges: age (+/- 10 years), gender, Maddrey function (<60; 60-90 and >90) and Lille score (+/-0.15).

• The overall optimal algorithm was able to select 3 unresponsive matched controls for 20 transplanted patients, 2 unresponsive matched controls for 3 transplanted patients and only 1 unresponsive matched control for 3 transplanted patients.

• The overall optimal algorithm was able to select 4 responsive matched controls for 21 transplanted patients, 2 responsive matched controls for 3 transplanted patients and only 1 responsive matched control for 2 transplanted patients.

Early LT in Alcoholic hepatitis

In transplanted 4 out of 5 deaths due to aspergillus infection

MELD score ≥ 24 at day 0 and ICU admission: Independent predictive factors of Aspergillus

T Gustot, J Hepatol 2014
Data On Alcohol Relapse in patients transplanted for severe alcoholic hepatitis

• No alcohol relapse within the 6 month period

• 3 patients resumed alcohol consumption during data collection
  - at 720, 740 and 1140 days
  - Despite counseling from addiction specialist, 2 patients remained daily consumers (30 g/day and > 50 g/wk, respectively) whereas 1 had occasional consumption (approximately 10 g/week)
Early LT in Alcoholic hepatitis

• 2 centers have prospective data base of severe alcoholic hepatitis
  - 14 out of 18 transplanted patients were referred by community hospitals
  - whereas only 4 patients (1.83%) were directly selected by the 2 centers from their own recruitment

• Proportions of eLT among the total number of procedures, and number of procedures for alcoholic liver disease, were 26/891 [2.92%]) and 26/315, [8.25%], respectively
Organ donation and early LT: does it matter?
In an era of organ shortage, use of liver transplants in severe AH may negatively affect the public attitude on transplantation and organ donation.

This may cause reluctance on the part of clinicians to modify guidelines for alcoholic patients.

However, healthcare practitioners must inform the public that patients with self-inflicted disease warrant the same access to medical resources as other patients.

Donckier V, Journal of Hepatology 2013
Effects of early liver transplantation on organ donation

An online survey created and distributed using Amazon Web Service’s mechanical Turk

<table>
<thead>
<tr>
<th>Category that best describes respondent’s prior experiences with transplantation</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior involvement with transplantation</td>
<td>414</td>
<td>82%</td>
</tr>
<tr>
<td>Family member of organ donor(s)</td>
<td>7</td>
<td>1.4%</td>
</tr>
<tr>
<td>Family member of organ recipient(s)</td>
<td>20</td>
<td>4.0%</td>
</tr>
<tr>
<td>Organ donor(^3)</td>
<td>45</td>
<td>8.9%</td>
</tr>
<tr>
<td>Healthcare professional (not physician) not involved with transplantation</td>
<td>11</td>
<td>2.2%</td>
</tr>
<tr>
<td>Nurse involved with transplantation</td>
<td>3</td>
<td>0.60%</td>
</tr>
<tr>
<td>Physician who is not involved with transplantation</td>
<td>3</td>
<td>0.60%</td>
</tr>
<tr>
<td>Physician involved with transplantation</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

Stroh G, American Journal of Transplantation 2015;
Effects of early liver transplantation on organ donation

An online survey created and distributed using Amazon Web Service’s mechanical Turk

<table>
<thead>
<tr>
<th>Action taken to indicate donor intent</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not taken any action</td>
<td>18</td>
<td>5.2%</td>
</tr>
<tr>
<td>Indicated on driver’s license</td>
<td>285</td>
<td>84%</td>
</tr>
<tr>
<td>Talked to family about wishes to donate</td>
<td>31</td>
<td>9.1%</td>
</tr>
<tr>
<td>Indicated on advanced directive or living will</td>
<td>5</td>
<td>1.5%</td>
</tr>
<tr>
<td>Placed name on donor registry</td>
<td>12</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

Stroh G, American Journal of Transplantation 2015;
Effects of early liver transplantation on organ donation

Stroh G, American Journal of Transplantation 2015;

Views on Early LT

- Strongly Disagree: 18%
- Neutral: 30%
- Agree or strongly agree: 51%
Effects of early liver transplantation on organ donation

Mean Approval Ratings of eLT Candidates by Selection Factors

<table>
<thead>
<tr>
<th>Table</th>
<th>Cohort</th>
<th>Good Financial Stability</th>
<th>Poor Financial Stability</th>
<th>p&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort</td>
<td>Good</td>
<td>6.08</td>
<td>5.81</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td></td>
<td></td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Good</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td></td>
<td></td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Good Social Support</th>
<th>Poor Social Support</th>
<th>p&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger-aged</td>
<td>6.07</td>
<td>5.79</td>
<td></td>
</tr>
<tr>
<td>Middle-aged</td>
<td>6.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Older-aged</td>
<td>5.73</td>
<td></td>
<td></td>
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</tbody>
</table>
Scientific Societies need to homogenize their guidelines according to data
Experts have to work at a homogenization of rules: European example

France

Practices of French Transplant Centers

- Yellow: Never Performed
- Red: Performed at least 1 procedure

Before 2011:
- 65% Never Performed
- 35% Performed

After 2011:
- 29% Never Performed
- 71% Performed

Antonini T, Liver Transplantation 2018
Experts have to work at a homogenization of rules: European example

France

Practices of French Transplant Centers
- Use 6-month rule
- 3-6 abstinence rule
- 1-3 abstinence rule

Before 2011:
- 29% Use 6-month rule
- 65% 3-6 abstinence rule
- 6% 1-3 abstinence rule

After 2011:
- 12% Use 6-month rule
- 59% 3-6 abstinence rule
- 29% 1-3 abstinence rule

Antonini T, Liver Transplantation 2018
Experts have to work at a homogenization of rules: European example

France

Practices of French Transplant Centres
- Addictologists during LT
  - Before 2011: 76%
  - After 2011: 88%
- Addictologists post-LT
  - Before 2011: 100%
  - After 2011: 100%

Antonini T, Liver Transplantation 2018
Experts have to work at a homogenization of rules: European example

Germany

Updated legal guidelines for LT in Germany:

• in exceptional cases transplant centers may request wait-listing for alcoholic patients abstinent for less than 6 months

• The request needs to be addressed to a committee of specialistst at the Bundesarztekammer

• These exceptional cases are defined underlies the responsibility of the requesting transplant center and the ethical judgment of the committee

Tacke F, Liver Transpl 2016
Experts have to work at a homogenization of rules: European example

Italy

Acute alcoholic hepatitis, end stage alcoholic liver disease and liver transplantation: An Italian position statement

Gianni Testino, Patrizia Burra, Ferruccio Bonino, Francesco Piani, Alessandro Sumberaz, Roberto Peressutti, Andrea Giannelli Castiglione, Valentino Patussi, Tiziana Fanucchi, Ornella Ancarani, Giovanna De Cerce, Anna Teresa Iannini, Giovanni Greco, Antonio Mosti, Marilena Durante, Paola Babocci, Mariano Quartini, Davide Mioni, Sarino Aricò, Aniello Basile, Silvia Leone, Fabiola Lozer, Emanuele Scafato, Paolo Borro

In a case of severe AAH, not responding to medical therapies

• LT is mandatory, even without achieving abstinence

• Italian pilot study started in 2017: around 6 patients have been transplanted for severe alcoholic hepatitis not-responding to medical therapy
Experts have to work at a homogenization of rules: European example

UK

before Brexit [do not worry before and after everything is open to discussion including early TH …]

NHSBT's James Neuberger told the Guardian: 'We transplant humans, not angels

transplant centres (Bathgate AJ, Lancet 2006)

Since 2014

The NHS Blood and Transplant Service is to offer alcoholics suffering from severe liver disease transplants for the first time
Experts have to work at a homogenization of rules: European example

In patients with severe ASH not responding to medical therapy, early LT is an efficient option but additional studies are required.

Journal of Hepatology 2018
Experts have to work at a homogenization of rules: Canadian example

ORIGINAL ARTICLE

Liver transplantation for alcoholic liver disease among Canadian transplant centres: A national study

Natasha Chandok MD MPH FRCPC1, Mohammed Aljawad MD FRCPC1, Angela White PhD2, Roberto Hernandez-Alejandro MD FRCPC3, Paul Marotta MD FRCPC1, Eric M Yoshida MD FRCPC4

Can J Gastroenterol Vol 27 No 11 November 2013

KEY MESSAGES

• Among the seven Canadian liver transplant programs, there is overall strong concordance in transplant policies toward patients with ALD with respect to adherence to the ‘six-month rule’ and no transplantation for severe acute alcoholic hepatitis.

• Canadian transplant policies regarding ALD are consistent with current American and European practices, but there is broad interest, particularly in Europe, toward further evaluation of LT in severe, medically refractory, acute alcoholic hepatitis in light of growing evidence of a survival benefit.
Experts have to work at a homogenization of rules: USA example
USA is evaluating Early Transplantation In Severe Alcoholic Hepatitis

Number of Early LT for Severe AH

Number of Transplant units listing Severe AH

Cholankeril G, Etats-Unis, AASLD 2017, Abs. 032 actualisé
American Evaluation of Early TH in severe AH

![Graph showing survival probability over time since LT](image)

- Probability of survival over time since LT (years)
- Alcohol use post-LT: Overall, No, Yes
- Time since LT (years)

Lee BP, Gastroenterology 2018
**American Evaluation of Early TH in severe AH**

**Table 3.** Univariate Risk of Overall Post–Liver Transplantation Death

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>More than 10 drinks/d at presentation</td>
<td>3.17 (1.04–9.67)</td>
<td>.04</td>
</tr>
<tr>
<td>Post-LT alcohol use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any alcohol use post-LT</td>
<td>3.54 (1.06–11.85)</td>
<td>.04</td>
</tr>
<tr>
<td>Sustained alcohol use post-LT&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.59 (1.45–14.54)</td>
<td>.01</td>
</tr>
</tbody>
</table>

Lee BP, Gastroenterology 2018
Improvement in selection of candidates for early LT
Null responders are the candidates for early LT?

Complete responders
Lille score ≤0.16 [≤35th percentile]

Partial responders
Lille score 0.16-0.56 [35-70th percentile]

Null responders
Lille score ≥0.56 [≥ 70th percentile]

Null responders are the candidates for early LT? [P Mathurin, Gut 2011]
Combining Data from Liver Disease Scoring Systems
outcome as a continuum in probabilities of death

Louvet A, Gastroenterology 2015
Control group
Alcoholic candidates for liver transplantation

AH not responding to medical therapy
Algorithm based on objective criteria
Range of Score from 0 to 250

Algorithm score ≥ 220
Selected

Algorithm score < 220
Not selected

Classical selection
6-month criteria

Primary objective
Non inferiority in terms of alcohol relapse

Secondary endpoint survival benefit

Not selected
Non responders Not Transplanted
Consultation meeting
- Evaluation of addiction specialist separately (note already assigned)
- Collegiate award points with need for a global consensus
- Notify date of this meeting and present.

Evaluation summary:
- If \(\text{score} \leq 200\) : Patient not considered as a candidate, will not be registered in transplant list
- If \(200 < \text{score} \leq 220\): A second assessment by addiction specialist and the team need to be done before final decision
- If \(\text{score} > 220\) : Patient candidate for transplant in accelerated procedure

Specific algorithm for encephalopathy patients
Evaluation of Family (Alcohol problem in relatives, relationship with patient

Psychiatric Evaluation

Coomordities

Addicaiton Evaluation
Conclusions

- After a first episode of alcoholic hepatitis, early liver transplantation may be proposed in non-responders as most deaths occur within 2 months in the watch-and-wait strategy.

- These encouraging results seem to be confirmed by other groups including American centers.

- International database collecting information on survival and addiction is warranted in order to provide more facts and less conjecture in future discussions of the role of early LT in treatment of severe alcoholic hepatitis.

- For this objective, French and Belgian centers devote themselves to test the algorithm for selection of candidates to early LT in alcoholic hepatitis (PHRC QuickTransHAA).
Research is rigorous learning, teaching and Friendship