Changing perspectives on acute alcoholic hepatitis and liver transplantation

Indications to liver transplantation and management of patients in the waiting list

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ELTR Indication to liver transplantation in periods 1988-1995 and 1996-2005

Burra Am J Transpl 2010
Alcohol relapse trajectories (DiMartini 2010)

- Abstinent
- Low amount infrequently
- Early onset, moderate use, decreasing
- Later onset, moderate use, increasing
- Early onset, heavy use, increasing
Time of alcohol relapse in 51 patients undergoing liver transplantation for alcoholic cirrhosis by duration of abstinence before transplantation

Miguet, Gastroenterol Clin Biol 2004
Patient and/or family awareness of alcoholism was the major risk factor for recurrence.

Overall alcohol relapse rate: 33%
Patterns of alcohol consumption following liver transplantation in HCV- vs HCV+ ALD recipients

<table>
<thead>
<tr>
<th>Patients</th>
<th>Abstainers (n=16)</th>
<th>Occasional drinkers (n=3)</th>
<th>Heavy drinkers (n=3)</th>
<th>Abstainers (n=7)</th>
<th>Occasional drinkers (n=4)</th>
<th>Heavy drinkers (n=1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericellular fibrosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score 0</td>
<td>42 (82)</td>
<td>13 (81)</td>
<td>5 (50)</td>
<td>14 (67)</td>
<td>9 (53)</td>
<td>2 (67)</td>
</tr>
<tr>
<td>Score 1-2</td>
<td>9 (18)</td>
<td>3 (19)</td>
<td>5 (50)</td>
<td>7 (33)</td>
<td>8 (47)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>Perivenular fibrosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score 0</td>
<td>36 (71)</td>
<td>12 (75)</td>
<td>7 (70)</td>
<td>10 (48)</td>
<td>8 (47)</td>
<td>1 (67)</td>
</tr>
<tr>
<td>Score 1-2</td>
<td>15 (29)</td>
<td>4 (25)</td>
<td>3 (30)</td>
<td>11 (52)</td>
<td>9 (53)</td>
<td>2 (33)</td>
</tr>
</tbody>
</table>

Burra Journal of Hepatology 2001
Rice Liver Transplantation 2013
Where is the focus today?

• The focus on recidivism due to alcohol rather than survival as the primary outcome after transplantation has been challenged.
  (Shawcross Lancet 2010)
Alcohol consumption impairs long-term survival after liver transplantation for alcoholic liver disease
Survival and pattern of alcohol relapse after liver transplantation

Log-rank P-value = 0.53

Tandon  Am J Gastroenterol 2009
Patient survival rates of patients who remained abstinent (n=234) and patients who resumed drinking (n=56) after liver transplantation

Piftzmann R. Liver Transpl 2007
Patient survival after liver transplantation according to liver disease in Europe (ELTR-ELITA data)

Burra P. Am J Transpl 2010
Medical complications as cause of death or graft failure following liver transplantation for alcoholic liver disease

<table>
<thead>
<tr>
<th></th>
<th>ALD (%)</th>
<th>VIRAL (%)</th>
<th>CRYP (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>15.5</td>
<td>15.7</td>
<td>17.6</td>
<td>ns</td>
</tr>
<tr>
<td>Rejection</td>
<td>7.6</td>
<td>6.7</td>
<td>10.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>8</td>
<td>5.3</td>
<td>7.6</td>
<td>0.0007</td>
</tr>
<tr>
<td>De Novo tumours</td>
<td>13.7</td>
<td>5.3</td>
<td>5.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Social</td>
<td>1.3</td>
<td>0.7</td>
<td>0.4</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Burra P. Am J Transpl 2010
Negative Impact of *De Novo* Malignancies Rather than Alcohol Relapse on Survival After Liver Transplantation for Alcoholic Cirrhosis: A Retrospective Analysis of 305 Patients in a Single Center
Alcoholic cirrhosis plus alcoholic hepatitis
Survival of patients transplanted for alcoholic cirrhosis and alcoholic cirrhosis plus alcoholic hepatitis

Impact of acute alcoholic hepatitis in the explanted recipient liver on outcome after liver transplantation

Wells JT, Liver Transpl 2007; 13(12):1728-35
Pretransplantation duration of abstinence

Wells JT, Liver Transpl 2007; 13(12):1728-35
Survival for patients with histologic acute hepatitis (AAH) vs cirrhosis (BAC)

Wells JT, Liver Transpl 2007; 13(12):1728-35
Graft survival in patients transplanted for alcoholic hepatitis (46) and alcoholic cirrhosis (138)


Alcoholic cirrhosis

P=0.97

Alcoholic hepatitis

Patient survival after transplantation for alcoholic hepatitis (46) and alcoholic cirrhosis (138)


P=0.90
Alcoholic hepatitis

• It is a distinct clinical syndrome that manifests as jaundice, abdominal pain, fever and acute hepatic decompensation of variable degrees depending on the severity of the disease.

• It may commonly be associated with underlying chronic liver disease.

• It is caused by excessive alcohol consumption of prolonged duration which is invariably heavy and increased in the last few weeks to months prior to presentation.

Liver transplantation and alcoholic hepatitis

Alcoholic hepatitis remains an absolute contraindication by most of the transplant centers.
(Bathgate AJ, Lancet 2006)

Liver transplantation has rarely proposed as a trasposition of current clinical practice for selecting patients with alcoholic cirrhosis which in many centres requires 6 months of abstinence.
(Burroughs J Hepatol 2012)

Severe alcoholic hepatitis has a mortality rate of 70% within 6 months if there is no response to supportive and steroid therapy.
(Louvet Hepatology 2007, Mathurin Gut 2011)
## Alcoholic hepatitis severity scores

<table>
<thead>
<tr>
<th>Severity score</th>
<th>On admission</th>
<th>Reference levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADDREY DISCRIMINANT FUNCTION</td>
<td>72</td>
<td>Severe disease ≥32</td>
</tr>
<tr>
<td>GLASGOW SCORE</td>
<td>10</td>
<td>Severe disease &gt;9</td>
</tr>
<tr>
<td>MELD SCORE</td>
<td>28</td>
<td>From &lt;9 to &gt;40</td>
</tr>
<tr>
<td>CHILD-PUGH GRADE</td>
<td>C-11</td>
<td>Grades A (5 to 6 points)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grades B (7 to 9 points)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grades C (10 to 15 points)</td>
</tr>
<tr>
<td>LILLE SCORE (at 7 days after steroid therapy)</td>
<td></td>
<td>≥0.45; null responder</td>
</tr>
</tbody>
</table>

Corticosteroids improve survival of patients with severe alcoholic hepatitis

Individual data analysis of 5 RCTs (Mendenhall, Carithers, Ramon, Cabre*, Philipps*)

Mathurin Gut 2011
Prednisolone 40mg/day for 7 days
Followed by Lille score calculation

EASL Guidelines
Journal of Hepatology 2011
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 Letoublon, 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.
Alcoholic hepatitis and transplantation

- Early liver transplantation in patients with severe alcoholic hepatitis non-responder to steroid treatment undergoing their first event of liver disease.

- Non responders were identified using Lille score ≥0.45 or worsening of liver function by day 7.

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

Selection process

The Kaplan–Meier estimates of survival in 26 patients

Alcoholic hepatitis and transplantation

• MELD at listing 34 (29-37)

• Risk of death after transplant related to fungal infections

• 3 patients relapsed
  • 720 days
  • 740 days
  • 1140 days

after liver transplantation

Where is the focus today?

• This paper challenges current medical practice because it demonstrates a dramatic survival benefit and the incrougrity of the 6-month rule.
Clinical Case
Padua Multivisceral Transplant Unit
March 20th, 2013

• MM, male, 52 years old, 85 Kg
• Ex football player

• Admitted to the hospital after the first episode of loss of consciousness in patient with jaundice, and concomitant increase in abdominal girth.

• Patient was unaware of liver disease.
# Blood test results

<table>
<thead>
<tr>
<th>Test</th>
<th>Value at admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (x10⁹)</td>
<td>12.9</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>10.6</td>
</tr>
<tr>
<td>MCV</td>
<td>109.3</td>
</tr>
<tr>
<td>PLTs (x10⁹)</td>
<td>141</td>
</tr>
<tr>
<td>PT (%)</td>
<td>25</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>74</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>21</td>
</tr>
<tr>
<td>Total Bilirubin (µmol/L)</td>
<td>338.3</td>
</tr>
<tr>
<td>Conjugated Bilirubin (µmol/L)</td>
<td>281.6</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>791</td>
</tr>
<tr>
<td>Alk Phos (U/L)</td>
<td>219</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>3</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>50</td>
</tr>
<tr>
<td>Na (mmol/L)</td>
<td>136</td>
</tr>
</tbody>
</table>
Steroid therapy: changes in bilirubin

- Prednisolone 40mg/day
- Tot Bil. (umol/L)
- Con Bil. (umol/L)

<table>
<thead>
<tr>
<th>March 22</th>
<th>March 23</th>
<th>March 25</th>
<th>March 27</th>
<th>March 29</th>
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<tbody>
<tr>
<td>374</td>
<td>410</td>
<td>368</td>
<td>415</td>
<td>442</td>
</tr>
<tr>
<td>318</td>
<td>347</td>
<td>331</td>
<td>354</td>
<td>388</td>
</tr>
</tbody>
</table>

March
Prognostic scores after 7 days of steroid treatment for severe alcoholic hepatitis

Lille Score: 0.84 ($>0.45$: null responder)
- 28 day survival: 53.3%

MELD score: 29
- 90 day survival: 47%
Liver transplantation
12th April 2013
MELD 42
Septal fibrosis
Cholestasis
Mallory bodies
One year post-transplant follow up

• Good liver function.
• Mild increase of creatinine.
• No alcohol intake.
• Good compliance.
Consensus on liver transplantation for alcoholic hepatitis

Ethical issues
• Natural justice.
• Shortage of donors.
• Deaths in the waiting list.

Medical aspects
• Risk of invasive aspergillosis.
• Risk of relapse.
Rationale for transplanting patients with alcoholic hepatitis

Transplanting patients with alcoholic hepatitis within strict and audited protocols allows equity and justice to be applied to these patients, whose alcohol behaviour may be no different to those with alcoholic cirrhosis alone, but who suffer an acute life threatening insult due to as yet unknown host/ alcohol/ environmental interactions.

Burroughs, 2010
Rescue liver transplantation for severe alcoholic hepatitis: arriving where we started?

- Alcoholic hepatitis remains excluded from the indications for liver transplantation until a new consensus emerges involving transplant hepatologists and surgeons, other members of the transplant team, and the public.

(Forrest and Lucey Hepatology 2013)
Ethical considerations regarding early liver transplantation in patients with severe alcoholic hepatitis not responding to medical therapy

Donkler et al J Hepatol 2014

“There are no major ethical barriers for further evaluation of new therapeutic option. The next step should include transparent communication with the public and further studies to reproduce the results and identify the selection criteria that provide the best long-term outcomes.”
Consensus on liver transplantation for alcoholic hepatitis

Societal level
• Transplantation performed in deliberate self harm.
  • Paracetamol overdose.
  • Ecstasy.
• Intravenous drug abusers.
• Unprotected sex.
“DELIBERATE EXCLUSION FROM TREATMENT SHOULD NOT BE BASED ON PREJUDICE, LACK OF EVIDENCE, OR PRESUMED LACK OF RESOURCE”

Burroughs, 2010
Consensus on liver transplantation for alcoholic hepatitis

Societal level

• Transplantation performed in deliberate self harm.
• Paracetamol overdose.
• Ecstasy.
• Intravenous drug abusers.
• Unprotected sex.
“Dependence or current alcohol and drug abuse represent an absolute contraindication to liver transplantation.”
Liver transplantation for severe alcoholic hepatitis to be proposed to A.I.S.F.

• Development of a nationally to be approved protocol:

(1) to allow a consistent approach to patients with severe alcoholic hepatitis, who might represent potential candidates for liver transplantation;

(2) to provide clinical data to better understand the role of early transplantation in the treatment of severe alcoholic hepatitis.