Liver Transplant:
Alcoholic liver disease as first indication

Giacomo Germani

Multivisceral Transplant Unit
Padova University Hospital
Cirrhosis as primary disease in Europe

- Alcoholic cirrhosis: 36.9%
- Virus-related cirrhosis: 33.6%
- Viral+Alcoholic cirrhosis: 7.8%
- Primary Biliary cirrhosis: 3.9%
- Cryptogenic cirrhosis: 3.9%
- Other: 8.4%
- Autoimmune cirrhosis: 1.4%
- Secondary biliary cirrhosis: 4.1%

http://www.eltr.org
Liver transplantation for alcoholic liver disease in Europe: a study from the ELTR

Ethical issues

- Self-inflicted disease
- Controversial view of the public
- Difficult to predict the rate of recidivism
- Risk of poor compliance

AND

- Shortage of donor organs
Assessing priorities for allocation of donor liver grafts: survey of the public and clinicians

- 17% of 1,000 members of the public
- 40% of 200 family Doctors
- 33% of 100 Gastroenterologists

thought that:

“the patient with alcoholic liver disease was the least deserving candidate”

Evaluation of the candidate for liver transplantation

Medical

Severity of liver disease (CPT, MELD, other...)

Prognosis

No contraindications

Psychosocial
Evaluation of the candidate for liver transplantation

Medical

Severity of liver disease (CPT, MELD, other...)

Prognosis

No contraindications

Psychosocial

- Alcohol abuse or dependence
- Polydrug abuse
- Amount and duration of alcohol consumption
- Alcohol abstinence
- Previous alcohol rehabilitation
- Social stability and family relationship
- Admission of alcoholism
Alcohol relapse after liver transplantation

«Any alcohol consumption» following liver transplantation

- **Lucey 1994**
  - Social drinking
  - Moderate drinking
  - Excessive drinking

- **Piftzmann 2007**
  - Minor lapse or slip
  - Sporadic drinking event followed by re-establishment of abstinence

- **Di Martini 2010**
  - Low levels/infrequent
  - Early onset, moderate but decreasing
  - Later onset, moderate but increasing
  - Early onset, heavy, increasing
Rate of alcohol relapse after liver transplantation

**Prospective studies**

- **Burra 2000**: 33%
- **Gish 2001**: 20%
- **Faure 2012**: 43.7%

**Retrospective studies**: rate of alcohol relapse from 13% to 50%
Risk factors for relapse

Young patients <44y more likely to drink again (Pageaux 1999)

Meta analysis of risk for relapse to substance misuse (Dew 2008):
• family history of alcohol dependence
• poor social support
• <6 months abstinence

Shorter prelisting abstinence correlates to shorter time to first drink post transplant (Tandon 2009)
6 month abstinence is not a robust criteria to predict alcohol relapse

Foster PF, Hepatology 1997
Abstinence and listing

There is NO 6 month rule.
Abstinence to exclude those who will not need LT.
Abstinence to assess alcohol addictive behavior.

“A 6–month abstinence before LT part of a larger strategy for management of alcohol dependence ...It should take into account time for motivation, achievement of abstinence and for prevention of relapse” (Liver Transplantation 2006).

6 month rule never adopted because lawyers determined that imposition of a 6-month rule was an indefensible position.
Patients with alcohol-related cirrhosis (+/- HCC) and expected survival >6 months

- 6-month abstinence period is an arbitrary definition, but still remains a valid criteria for this subset of patients, mainly because it allows to evaluate potential improvement in liver function.

- All patients should undergo a multidisciplinary evaluation to identify risk factors for non-adherence.

- If the stability of liver disease has not been achieved within 6 months, evaluation for liver transplantation can be started. If liver function get worse, liver transplantation is indicated even without 6 months of abstinence.
AISF Position Paper

Patients with alcohol-related cirrhosis (+/- HCC) and expected survival <6 months

• In this subset of patients, the 6-month abstinence period does not represent a requirement for LT, as liver decompensation is the priority compared to the pre-LT length of sobriety.

• All patients should undergo a multidisciplinary evaluation performed by addiction specialist, psychiatrist, psychologists and social worker in order to identify risk factors for non-adherence before and after LT.

Patient survival after liver transplantation for cirrhosis in Europe (ELTR-ELITA data)
Survival by post-transplant drinking status

Log-rank P-value = 0.53

Tandon  Am J Gastroenterol 2009
Excessive alcohol consumption after liver transplantation impacts long-term survival, regardless of the primary indication.

![Survival Probability Graph](image-url)

- **No alcohol**
- **Excess alcohol**

Faure J Hepatol 2012
Cause of death or graft failure in patients transplanted for alcoholic liver disease

<table>
<thead>
<tr>
<th>Cause</th>
<th>ALD</th>
<th>VIRAL</th>
<th>CRYPT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>16%</td>
<td>16%</td>
<td>17%</td>
<td>ns</td>
</tr>
<tr>
<td>Rejection</td>
<td>8%</td>
<td>7%</td>
<td>10%</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td><strong>8%</strong></td>
<td>5%</td>
<td>7%</td>
<td>0.0007</td>
</tr>
<tr>
<td>De novo neoplasm</td>
<td>14%</td>
<td>5%</td>
<td>6%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Social</td>
<td>1%</td>
<td>1%</td>
<td>0.4%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Risk of cardiovascular events after liver transplantation for alcoholic cirrhosis

- Risk of cardiovascular events after liver transplantation = 10% of patients experience 1 or more events.
- Higher risk in patients with alcohol relapse.
- Worse 10-year survival.
- 40% of deaths attributed to cardiovascular events.

Albeldawi Liver Transpl 2012; Cuadrado Liver Transpl 2005
Metabolic syndrome after liver transplantation

<table>
<thead>
<tr>
<th>Predictors of MetS by IDF</th>
<th>OR</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Shorter time from LT</td>
<td>1.03</td>
<td>1.01-1.03</td>
</tr>
<tr>
<td>Older age</td>
<td>1.08</td>
<td>1.04-1.13</td>
</tr>
<tr>
<td><strong>Alcoholic liver disease</strong></td>
<td><strong>3.88</strong></td>
<td><strong>1.43-10.51</strong></td>
</tr>
<tr>
<td>BMI &gt;25 before LT</td>
<td>6.17</td>
<td>2.56-14.89</td>
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<tr>
<td>Reduction of physical activity as cause of weight gain after LT</td>
<td>7.10</td>
<td>1.71-29.5</td>
</tr>
<tr>
<td>Reduced calcium intake</td>
<td>7.73</td>
<td>1.75-34.23</td>
</tr>
</tbody>
</table>

Anastacio LR, Nutrition 2011
Cause of death or graft failure in patients transplanted for alcoholic liver disease

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<tr>
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<td>1%</td>
<td>1%</td>
<td>0.4%</td>
<td>0.03</td>
</tr>
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De novo cancer after liver transplantation according to underlying liver disease
Negative impact of *de novo* malignancies rather than alcohol relapse on survival after liver transplantation for alcoholic cirrhosis

Retrospective analysis on 305 patients

\[ p < 0.0001 \]
Multivariate analysis of the risk factors for solid organ malignancy

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>HR (95%CI)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Age by decade</td>
<td>1.33 (1.05-1.66)</td>
<td>0.014</td>
</tr>
<tr>
<td><strong>Smoking history</strong></td>
<td><strong>1.72 (1.06-2.79)</strong></td>
<td><strong>0.029</strong></td>
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<tr>
<td>ALD</td>
<td><strong>2.14 (1.22-3.73)</strong></td>
<td><strong>0.007</strong></td>
</tr>
<tr>
<td>PSC</td>
<td>2.62 (1.50-4.56)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Watt K. Gastroenterology 2009
Quality of life before and one year after liver transplantation

LEIPAD
- Total
- Alcohol
- HCV

Months post-OLT

* p<0.05 vs pre-OLT
§ p<0.05 vs total and ALD

Burra P, et al. AGEB 2005
Employment status after liver transplantation

Hartl J. Scan J Gastroenterol 2011
Mean International Index Erectile Function score in liver transplanted male patients

![Bar chart showing mean IIEF scores for Wellbeing, Satisfaction, Libido, Orgasm, and Erection. The chart compares Alcohol-related and Non alcohol-related scores.](image)

\[ p=ns \]

Mean Female Sexual Function Index (FSFI) score in liver transplanted female patients

- Distress
- Pain
- Satisfaction
- Orgasm
- Lubrification
- Arousal
- Desire
- FSFI tot

Alcohol-related: p=0.04
Viral-related: p=0.04
Other aetiologies

Non-adherence after liver transplantation according to liver disease aetiology

- IS therapy: 43% Alcohol, 47% Non Alcohol
- Outpatient clinic: 53% Alcohol, 47% Non Alcohol
- Blood tests: 44% Alcohol, 56% Non Alcohol

Burra P. & Germani G. Liver Transpl 2010
Natural history of alcoholic liver disease

Chronic alcohol misuse → Steatosis 90-95%

Hepatitis → Fibrosis 40-50%

Fibrosis → Cirrhosis 10-20%

Cirrhosis → HCC 8-20%

Hepatitis 40-50%

Fibrosis 10-20%

Cirrhosis 8-20%

HCC 3-10%
Natural history of alcoholic liver disease

Chronic alcohol misuse → Steatosis (90-95%)

Hepatitis → Fibrosis (40-50%) → Cirrhosis (10-20%)

Cirrhosis → HCC (8-20%)

HCC → Cirrhosis (3-10%)
Incidence rate per $10^6$ population per year 1999–2003 and 2004–2008

Sandahl TD, J Hepatol 2011
28-day and 84-day mortality (1999–2008)

Mortality (%)

(84 day)

(28 day)

Women

Men


Sandahl TD, J Hepatol 2011
Liver transplantation for alcoholic hepatitis

- Alcoholic hepatitis remains an absolute contraindication by most of the transplant centers.

- Liver transplantation has rarely proposed as a transposition of current clinical practice for selecting patients with alcoholic cirrhosis.

- Severe alcoholic hepatitis has a mortality rate of 70% within 6 months if there is no response to therapy.

Bathgate AJ. Lancet 2006; Burroughs AK. J Hepatol 2012
Louvet Hepatology 2007, Mathurin P. Gut 2011
Impact of AAH in the explanted recipient liver on outcome after liver transplantation

• 148 LT patients for ALD:
  Cirrhosis + AAH (n=32)
  Cirrhosis (n=116)

• Pre-transplant abstinence:
  0-6 months = 28%
  6-12 months = 26%
  >12 months = 46%

Wells JT, Liver Transpl 2007
Graft and patient survival after liver transplantation for AAH and ALD

- UNOS cohort

- 5 year graft (p=0.97) and patient (p=0.90) survival not different between alcoholic hepatitis and alcoholic cirrhosis.

- No differences based on diagnosis of the explant, at listing, explant.

Singal AK, Hepatology 2012
Early Liver Transplantation for Severe Alcoholic Hepatitis

- Patients with severe AH - first event of liver disease.

- Non responders were identified using Lille score ≥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

Survival in the 26 Study Patients and the 26 Best-Fit Matched Controls

Survival among the 26 study patients and randomly selected controls
Alcohol relapse after liver transplantation

- No alcoholic relapse within the first 6-months

- 3/26 (11.5%) patients later resumed drinking alcohol:
  - 1 patient at 720 days
  - 1 patient at 740 days
  - 1 patient at 1140 days

- After counseling by addiction specialist:
  - 2 patients remained daily consumers
  - 1 drank occasionally

- None has had graft dysfunction
Validation of the Procedure of Early Liver Transplantation in Alcoholic Hepatitis Resisting to Medical Treatment (QuickTrans) (NCT01756794)

Multicentre French-Belgian Study

**Primary Endpoint**

To demonstrate that alcohol relapse within the 2-year follow-up period in patients selected for early liver transplantation for severe alcoholic hepatitis is not inferior to that of patients transplanted for alcoholic cirrhosis using the 6-month sobriety period.
Early Liver Transplantation for Severe Alcoholic Hepatitis in the US - A Single Center Experience

- Survival compared between those receiving early liver transplantation and matched patients who did not.
- **94 patients** with severe AH not responding to medical therapy were evaluated for early liver transplantation.
- 9/94 (9.6%) candidates underwent liver transplantation.
Survival in 9 early liver transplant recipients and 9 matched controls

1 alcohol relapse

Three-year Results of a Pilot Program in Early Liver Transplantation for Severe Alcoholic Hepatitis

43 patients underwent liver transplant since 2015
- 17/43 with acute alcoholic hepatitis
- 26/43 with alcoholic cirrhosis and ≥6 month abstinence

<table>
<thead>
<tr>
<th></th>
<th>Acute Alcoholic Hepatitis (n=17)</th>
<th>Alcoholic Cirrhosis (n=26)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>1.5</td>
<td>1.6</td>
<td>ns</td>
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<tr>
<td>Post-transplant hospital stay (days)</td>
<td>18 (7-51)</td>
<td>12.5 (4-133)</td>
<td>ns</td>
</tr>
<tr>
<td>6-month survival</td>
<td>17 (100%)</td>
<td>23 (88.5%)</td>
<td>ns</td>
</tr>
<tr>
<td>Any alcohol relapse</td>
<td>4 (23.5%)</td>
<td>7 (29.2%)</td>
<td>ns</td>
</tr>
<tr>
<td>Alcohol relapse with harmful patterns</td>
<td>4 (23.5%)</td>
<td>3 (11.5%)</td>
<td>ns</td>
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</table>

# Liver Transplantation for Alcoholic Hepatitis: A Survey of Liver Transplant Centers

<table>
<thead>
<tr>
<th>Center</th>
<th>Total</th>
<th>For AAH</th>
<th>First AAH</th>
<th>NRS</th>
<th>PSS</th>
<th>Contract</th>
<th>Recidivism</th>
<th>6mo</th>
<th>1yr</th>
<th>5yrs</th>
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<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>2 (2%)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>2</td>
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<td>5 (1.3%)</td>
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<td>Yes</td>
<td>No</td>
<td>No</td>
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<td>5</td>
<td>5</td>
<td>4</td>
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<tr>
<td>3</td>
<td>500</td>
<td>7 (1.4%)</td>
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<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>1</td>
<td>7</td>
<td>7</td>
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<tr>
<td>4</td>
<td>350</td>
<td>2 (0.6%)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>0</td>
<td>2</td>
<td>NA</td>
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<td>5</td>
<td>225</td>
<td>2 (0.9%)</td>
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<td>Yes</td>
<td>Yes</td>
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<td>6</td>
<td>45</td>
<td>3 (6.7%)</td>
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<td>3</td>
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<td>7</td>
<td>150</td>
<td>3 (2%)</td>
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<tr>
<td>8</td>
<td>645</td>
<td>15 (2.3%)</td>
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<td>Yes</td>
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<td>15</td>
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<td>9</td>
<td>425</td>
<td>3 (0.7%)</td>
<td>No</td>
<td>Yes</td>
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<td>No</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>NA</td>
</tr>
</tbody>
</table>

NRS: non response to steroids; PSS psychosocial support

Hasanin M et al. Liver Transpl 2015
Early liver transplantation for acute alcoholic hepatitis

- Program started at Multivisceral Transplant Unit (Padua University Hospital) in 2013.

- **9 patients** with severe AH evaluated for liver transplantation.
- 5/9 patients respected the selection criteria.
- 4/9 patients excluded due to psychosocial contraindication
  - 2/4 died within 28 days
  - 2/4 still alive.

- **4/5 suitable patients underwent liver transplantation**
  - 1/5 died during the evaluation process.
- 4/4 patients alive with no alcohol relapse at a median follow-up of 17 months (range 9-41 months).

Burra P. & Germani G. Clinical Liver Disease 2016
Liver transplantation for alcoholic hepatitis

Issues

**Medical**
- Risk of relapse

**Societal**
- Public views
- Effect on organ donation

**Ethical**
- Natural justice
- Shortage of donors
- Deaths in the waiting list
Liver transplantation for alcoholic hepatitis

- Deliberate exclusion from treatment should not be based on prejudice, lack of evidence, or presumed lack of resource.

- Transplanting patients with AAH within strict and audited protocols allows equity and justice to be applied to these patients.

- AAH 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.

Burroughs AK. J Hepatol 2010; Forrest & Lucey Hepatology 2013
AISF Position Paper

Is acute alcoholic hepatitis, as first event of decompensation in patient with chronic liver disease, an indication to liver transplantation?

• Only if the following criteria are respected:
  – absolute consensus of paramedical and medical staff
  – no co-morbidities
  – social integration
  – supportive family members
  – psychiatric evaluation and addictive profile

• For patients not suitable for steroid therapy liver transplantation can be considered only if they respect the above criteria.
Conclusions (I)

- Alcoholic liver disease is an established indication for liver transplantation with good long-term patient and graft survival.

- Alcohol recidivism is reported in at least 1/3 of recipients, but alone is not an important cause of graft pathology or failure (coexistent conditions should be evaluated).

- Interventions to avoid the development of features of metabolic syndrome and de novo tumors should be directed towards these recipients.
Conclusions (II)

- After a 1st episode of liver decompensation, early liver transplantation may be proposed in NRS without any therapeutic option.

- Despite early liver transplantation challenges the 6-month abstinence rule, the present results support future evaluation in drastically selected NRS.

- In an era of organ shortage, use of liver transplants in severe AH may negatively affect the public attitude on transplantation and organ donation.
Is acute alcoholic hepatitis, as first event of decompensation in patient with chronic liver disease, an indication to liver transplantation?

- Diagnosis of acute alcoholic hepatitis is mainly based on clinical evaluation, however trans-jugular liver biopsy should be performed, when available, and in centres with high experience (4, C).
- The histological diagnosis does not represent a requested criteria for steroid therapy (4, C).
- The presence of infections and/or sepsis should always be excluded before starting steroid therapy (2b, B).
- Steroid therapy should be performed in patients with a DF ≥32 and should be based on methylprednisolone 40mg/day (2b, B).
- When the patient is a potential candidate for LT, steroid therapy should always be performed in a liver transplant centre (5, D).
Survival rates of patients who remained abstinent (n=234) and patients who resumed drinking (n=56)
28-day survival according to treatment with corticosteroids or non-corticosteroids

However

20% are dead at 2 months
40% are dead at 6 months
even when steroids given