

WJG 20<sup>th</sup> Anniversary Special Issues (10): Alcoholic liver disease**Acute alcoholic hepatitis, end stage alcoholic liver disease and liver transplantation: An Italian position statement**

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**Abstract**

Alcoholic liver disease encompasses a broad spectrum of diseases ranging from steatosis steatohepatitis, fibrosis, and cirrhosis to hepatocellular carcinoma. Forty-four per cent of all deaths from cirrhosis are attributed to alcohol. Alcoholic liver disease is the second most common diagnosis among patients undergoing liver transplantation (LT). The vast majority of transplant programmes (85%) require 6 mo of abstinence prior to transplantation; commonly referred to as the "6-mo rule". Both in the case of progressive end-stage liver disease (ESLD) and in the case of severe acute alcoholic hepatitis (AAH), not responding to medical therapy, there is a lack of evidence to support a 6-mo sobriety period. It is necessary to identify other risk factors that could be associated with the resumption of alcohol drinking. The "Group of Italian Regions" suggests that: in a case of ESLD with model for end-stage liver disease < 19 a 6-mo abstinence period is required; in a case of ESLD, a 3-mo sober period before LT may be more ideal than a 6-mo period, in selected patients; and in a case of severe AAH, not respond-

ing to medical therapies (up to 70% of patients die within 6 mo), LT is mandatory, even without achieving abstinence. The multidisciplinary transplant team must include an addiction specialist/hepato-alcoholologist. Patients have to participate in self-help groups.

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**Key words:** Alcohol; Alcoholic hepatitis; Cirrhosis; Hepatocellular carcinoma; Liver transplantation

**Core tip:** Alcoholic liver disease is the second most common diagnosis among patients undergoing liver transplantation. The vast majority of transplant programmes (85%) require 6 mo of abstinence prior to transplantation; commonly referred to as the “6-mo rule”. The “Group of Italian Regions” suggests a reduction of the waiting period in some cases. The multidisciplinary transplant team must include an addiction specialist/hepato-alcoholologist. Patients have to participate in self-help groups.

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## INTRODUCTION

Every organ and system in the human body is harmed to some degree by alcohol. Medically speaking, the nervous, circulatory and hepato-gastroenterological systems suffer the most damage<sup>[1]</sup>. The connection between alcohol abuse and liver disease has been known about for centuries. Liver damage can present as a wide range of alcoholic liver diseases (ALD): simple liver damage, fatty liver, steatohepatitis, fibrosis, hepatocellular carcinoma (HCC), or cirrhosis.

There are many pathognomonic histological features of ALD. These include steatosis (caused by the diversion of metabolic reducing equivalents from the conversion of ethanol into acetate, and then into fatty acids and triglyceride synthesis); ballooning degeneration (this is when the plasma membrane loses osmo-regulatory control); Mallory body formation (when intracellular cytokeratin microfilaments become condensed into skeins of clumped intracellular protein); inflammation, largely neutrophilic within the parenchyma but may also occur as mixed inflammation inside the portal tracts; fibrosis; and regeneration which is less common in ALDs than in other forms of hepatitis. The three major scarring types most commonly found in human ALD are centrilobular

scarring, pericellular fibrosis, and periportal fibrosis. Progressive liver fibrosis leads to alcoholic cirrhosis<sup>[1,2]</sup>.

## ALD: ACTIONS LEADING TO LIVER DAMAGE

Alcohol abuse causes liver damage directly due to oxidative stress, inflammation, and endotoxins<sup>[1,3]</sup>.

The progression of ALD is specifically connected to an increase in intestinal permeability and, as a result, to endotoxemia. Ethanol and acetaldehyde have a negative effect on epithelial tight junctions in the intestine, thus increasing intestinal permeability to endotoxins.

Endotoxemia leads to hepatic damage in two ways. First, it causes Kupffer cells to secrete reactive oxygen intermediates and cytokines. Second, and more importantly, it affects the hepatic sinusoids, thus increasing vascular permeability.

These inflammatory substances, for example tumor necrosis factor alpha (TNF- $\alpha$ ), along with a higher incidence of TNF- $\alpha$  receptors, could lead to further liver damage. High levels of TNF- $\alpha$  have been well documented as being related to a poor prognosis.

Cellular oxidative-stress (caused by an imbalance between the generation of free radicals generation and a lack of anti-oxidant defence mechanisms, and which includes a reduction in phosphatidylcholine, vitamin E and glutathione), together with endotoxemia, act as catalysts to the progression of steatohepatitis into hepatic necrosis, fibrosis, and cirrhosis.

20%-40% of patients with steatosis have liver biopsy results indicating alcoholic steatohepatitis. Therefore, steatosis along with hepatocellular damage is associated with both inflammation and fibrosis.

Any reversal of steatohepatitis, once it has developed, has been found to be rare, and the risk of cirrhosis increases significantly.

Following damage to the liver, the hepatic stellate cells (HSCs) go through a transition called “activation,” which is when quiescent cells transform into proliferative, fibrogenic, and contractile myofibroblasts. So, once activated, HSCs react to different outside pressures in both an autocrine and paracrine way in order to proliferate, migrate and contract; they secrete extracellular matrix components, chemokines, cytokines, proteases, and growth factors. They also express transcription factors and signalling molecules<sup>[1]</sup>.

These HSC are crucial in the control of sinusoidal tone and blood flow. They have a tendency to cause contraction, which slows portal blood flow and increases vascular resistance during the occurrence of fibrosis and cirrhosis. Endothelin-1 (ET-1) is the main cause of contraction in activated stellate cells.

There is an increase in the expression of ET-1 and a decrease in the production of nitric oxide (NO) in liver fibrosis due to the occurrence of sinusoidal endothelium, thus creating more favourable conditions for stellate cell contractility<sup>[1,2]</sup>.

## ALD: HOST FACTORS AND COMORBIDITIES

There is no clear linear relationship between the volume of alcohol ingested and the progression of liver disease.

Alcohol-mediated hepatotoxicity has been found to affect women twice as much as men, and so women may present more severe ALD over a shorter period of time and with lower levels of alcohol consumption than men.

The risk of developing cirrhosis increases with the consumption of more than 60-80 g/d of alcohol for  $\geq$  10 years in men, and more than 20 g/d in women<sup>[3,4]</sup>.

The chances of developing lesser degrees of liver disease or cirrhosis with a daily alcohol consumption of more than 30 g/d are 13.7 and 23.6, respectively, when compared with non-drinkers<sup>[5]</sup>.

The following results of a meta-analysis were recently published by The European Association for the Study of the Liver (EASL): it was found that there was an increased risk of death from liver cirrhosis in men and women drinking 12-24 g of ethanol per day. They also discovered a significant increase in this risk for women drinking up to 12 g/d<sup>[6]</sup>. These are the recommended safe levels of alcohol ingestion (< 25 g/d), and are significantly lower than most public health advice for what are widely considered to be safe levels of alcohol intake. The EASL came to the conclusion that if a safe level of alcohol consumption can be quantified, it is very low, and may be difficult to measure due to limitations in measuring an intake of below 10-12 g per day.

It was recently found that even a relatively low alcohol intake can cause ALD which requires liver transplantation (LT)<sup>[7]</sup>. It was also indicated that consuming alcohol outside of meal times can increase the risk of ALD by 2.7-fold in comparison with people who drink alcohol only with their meals<sup>[8]</sup>.

It has also been demonstrated that binge drinking increases the risk of ALD and mortality<sup>[7]</sup>.

Several significant independent risk factors are also present: obesity, visceral fat, hyperlipidaemia, diabetes and insulin resistance, metabolic syndrome, hepatitis viruses [mostly hepatitis B virus (HBV) and hepatitis C virus (HCV)] and Pearls grade<sup>[1]</sup>.

It has also been demonstrated that body mass index (BMI) and fasting blood glucose concentrations are other independent risk factors for fibrosis in liver disease caused by alcohol consumption<sup>[9]</sup>. Pearls grade has also been independently correlated with the fibrosis score. Being overweight or obese significantly increases susceptibility to endotoxin liver damage. It has been well documented that there is a close correlation between endotoxemia and the severity of liver damage due to alcohol ingestion.

70%-90% of all cases of liver disease in Western countries are due to infection with chronic hepatitis C virus, for which alcohol consumption is responsible. Furthermore, 8%-43% of patients with ALD also test positive for anti-HCV<sup>[1]</sup>.

In terms of the histological and clinical progression of HCV infection, alcohol consumption is one of the main risks. Ethanol and HCV were recently shown to act in combination to alter the liver's antioxidant defences and to increase the formation of free radicals. This study also demonstrated that moderate alcohol intake (< 50 g/d) and heavy consumption (> 50 g/d) increase the chance of developing oxidative stress by 3 times and by 13-24 times, respectively<sup>[10]</sup>. HCV and ethanol assumption were demonstrated in a further study to increase hepatic lipid peroxidation. Moreover, they synergistically increase the incidence of hepatic TNF- $\alpha$  and tumor growth factor (TGF)- $\beta$ <sup>[10]</sup>. TGF- $\beta$  causes the activation of HSC, which leads to extracellular matrix overproduction. The occurrence of TNF- $\alpha$  also involves reactive oxygen species formation, which can lead to an increase in hepatic fibrosis.

The effects of alcohol on serum HCV-RNA have been widely reported and have shown some conflicting evidence. Some reports state that a higher viral load can be caused by chronic ethanol ingestion. Conversely, other reports discovered no clear relationship between alcohol consumption and HCV-RNA.

Furthermore, a downturn in patients' responses to antiviral therapy in chronic hepatitis C was also associated with alcohol intake<sup>[11]</sup>.

A significant correlation between alcohol consumption, viral hepatitis, diabetes mellitus, and BMI was also shown by Hassan *et al*<sup>[11]</sup>.

Patients with a heavy alcohol intake (> 80 g/d) who had chronic viral hepatitis (HBV or HCV) presented an odds ratio (OR) of 53.9 (the virus alone was OR = 19.1, alcohol alone was 2.4), and those patients with a high level of alcohol consumption who had diabetes (insulin-dependent or non-insulin-dependent) presented an OR of 9.9 (the diabetes alone was 2.4)<sup>[1,12-14]</sup>.

Alcohol drinkers who have a BMI of 30 kg/m<sup>2</sup> or more have a 3.1 times greater risk of developing incident HCC as compared with non-drinkers with a BMI of less than 30 kg/m<sup>2</sup>; this could well be a synergic effect. The risk of incident HCC in alcohol drinkers who are obese is much higher than in non-drinkers<sup>[13]</sup>.

Recently, French *et al*<sup>[15]</sup> found evidence of the role played by the Toll-like receptor (TLR), which triggers the mechanism of the transformation of liver stem cell/progenitors into HCC. This mechanism is the cause behind alcohol intake increasing the risk of incident HCC in cases of hepatitis C, hepatitis B, diabetes and obesity. This synergism is due to the activation of a common pathway: signals from the TLR trigger the production of both pro-inflammatory cytokines (as nuclear factor- $\kappa$ B activation) and growth factors (*via* the stimulation of activator protein 1).

Out of the several host factors that could be linked to the various types of ALD, the most research has gone into genetic determinants, or the so-called susceptibility genes<sup>[16]</sup>.

Some genetic variations have already been described: genes coding for alcohol-metabolizing enzymes, genes with some relation to oxidative stress, genes involved in



immune reactions, genes coding for factors related to fibrosis and genes which take part in modulating steatosis<sup>[16]</sup>.

## END STAGE LIVER DISEASE AND LIVER TRANSPLANTATION

Those patients with cirrhosis who continue to drink have a 5-year life expectancy of less than 70%, although this increases to 90% if they do not consume any more alcohol. For those patients with decompensated cirrhosis who no longer drink alcohol, they have a life expectancy of more than 50%, but this falls to less than 30% if they continue to consume alcohol<sup>[1]</sup>.

It was recently proved that refraining from drinking alcohol one month after diagnosis is one of the main factors for the survival of patients with cirrhosis; for abstainers there is a 72% chance of a 7-year life expectancy, but only 44% for patients who continue to drink. Verrill *et al*<sup>[17]</sup> have confirmed through biopsy that it is never too late to stop alcohol consumption, even in the later stages of cirrhosis<sup>[18]</sup>.

Eighty percent of deaths from liver disease are attributed to alcohol. Deaths from cirrhosis caused by alcohol stand at 44%<sup>[4]</sup>. ALD is the second most common factor in patients having a LT in the United States and in Europe.

Burra *et al*<sup>[19]</sup> found a rise in LTs attributed to alcohol. They collected and analysed data from: 9880 patients who underwent a transplant for ALD; 10943 with viral cirrhosis (6672 with HCV, 3579 with HBV and 584 with HCV-HBV combined); 1478 patients who had ALD as well as a viral infection; and 2410 with cryptogenic cirrhosis. They excluded 108 patients who were infected with hepatitis viruses other than HBV and HCV. They observed that the number of patients undergoing an LD for ALD with or without concomitant viral infection increased significantly between 1988 and 1995, and between 1996 and 2005. This was linked to an associated drop in the percentage of transplants performed for cryptogenic cirrhosis (14.3% *vs* 8%,  $P < 0.001$ )<sup>[18,19]</sup>.

Some data was recently reported supporting LTs in cases of ALD.

Most transplants (85%) routinely require 6 mo of zero alcohol consumption before the operation; this is known as the “6-mo rule.” This rule became a general requirement in 1997, when the United Network for Organ Sharing (UNOS) had a meeting to discuss the criteria as to how adult patients are selected for placement on a liver transplant waiting list<sup>[20]</sup>.

The UNOS broadly agreed on this requirement, although they did not make it absolute and advised “exceptional” cases be referred to “regional review boards for consideration”<sup>[20]</sup>.

The American Association for the Study of Liver Disease (AASLD) recent guidelines also advise 6 mo of zero alcohol consumption before a LT, but they emphasised that this rule as it stands is not a defining factor as to whether a patient is accepted as a candidate for a liver transplant<sup>[18,20]</sup>.

It has been shown that patients who have undergone a liver transplant for ALD have a slightly higher life expectancy compared to those with viral etiologies, and a much greater unadjusted life expectancy overall when compared to liver transplant patients with cryptogenic cirrhosis<sup>[19]</sup>. The proportion of alcoholic patients who suffered a recurrence of their disease leading to death or graft failure was only 4%. After a liver transplantation for ALD, acute and chronic cellular rejections are not common<sup>[18,21,22]</sup>. The most common causes of death in those patients who continued to consume alcohol were cardiovascular events and cancer, and not liver failure directly caused by alcohol consumption.

Several studies have indicated that patients with HCV and ALD have similar graft and life expectancies as those who have undergone transplantation for either HCV or ALD alone<sup>[23,24]</sup>.

There is evidence that patients with ALD and HCV have a much lower life expectancy than those with both ALD and the HBV infection<sup>[19]</sup>.

From an evaluation of 12 selected studies, two showed that a 6-mo abstinence period was one factor linked to a relapse to alcohol consumption<sup>[24]</sup>.

In a 2008 meta-analysis, fifty trials researching the predictors of relapse in alcoholic transplant patients were studied and one major cause of patients consuming more alcohol was an abstinence of fewer than 6 mo before the operation<sup>[20,25]</sup>.

On the other hand, it has been demonstrated that many carefully chosen patients with ALD have shown that even if they stick to the 6-mo rule, there are still high rates of alcoholic relapse<sup>[20]</sup>. Although, with each additional month of pre-transplant abstinence, the risk of relapse after the transplant decreases by 33%<sup>[20,26]</sup>. They were not able to pinpoint the clinical cut-off point that would guarantee abstinence after an LT.

Evidence has also been found that the 5-year life expectancy in anti-HCV-positive and anti-HCV-negative patients affected by ALD was similar (69.9% and 72%, respectively)<sup>[27]</sup>. Post-transplantation, 10%-21% of HCV-positive patients suffered fibrosis or cirrhosis within 5 years. It has also been recently demonstrated that there is no difference in life expectancy between alcoholics and non-drinkers after a LT<sup>[28]</sup>.

A study was recently carried out which involved collecting urine samples in order to measure urinary ethyl glucuronide (EtG) from ALD patients about to undergo liver transplantation. Fifty percent had consumed alcohol at least once during the group therapy stage, but they neither admitted this when asked, nor was it proved by alcohol breath testing<sup>[29]</sup>.

If we take all these trials into consideration, in theory at least, 5 years of not consuming alcohol may be the best predictor of zero post-transplant relapse. Although, unfortunately, patients with decompensated ALD waiting for an LT rarely achieve this outcome.

We can therefore conclude that the 6-mo period of zero alcohol consumption does not guarantee abstinence,

which may have an impact on patients who abstain despite a shorter period of not consuming alcohol before their LT<sup>[20]</sup>.

## CLINICAL FEATURES OF ACUTE ALCOHOLIC HEPATITIS: ITS MANAGEMENT AND TRANSPLANT

Jaundice and liver failure are symptoms of alcoholic hepatitis (AH) that mostly present after decades of heavy alcohol consumption<sup>[30]</sup>.

Patients with acute alcoholic hepatitis may have symptoms clinically similar to those with decompensated cirrhosis, and it is therefore difficult to determine if they also have associated cirrhosis. Histologically, most patients with acute AH generally have either significant fibrosis or cirrhosis of the liver.

The average age of a patient diagnosed with AH is approximately 50 years. The actual number of patients with AH is not known. The occurrence of AH in liver biopsy patients is around 20%, and it may be in 10%-35% of alcoholic patients in hospital<sup>[31]</sup>.

Mild and moderate forms of acute AH (AAH) often respond to complete cessation of alcohol consumption, while the prognosis for patients with severe AAH is poor; as many as 70% die within 6 mo.

One effect of severe AAH, even when cirrhosis is not present, is that the main (portal) vein bringing blood from the intestine and stomach into the liver can experience increased pressure due to scarring of the liver, thus leading to portal vein hypertension and various complications<sup>[1,32]</sup>.

The ability to provide a prognosis for any given patient is critical when making decisions about the treatment.

The Maddrey discriminant function (DF) has been used in AH cases to grade the severity of a patient's illness. The initial formula came as a result of clinical trials of AH, and was subsequently modified to: 4.6 (patient's prothrombin time PT-control prothrombin time PT) + total bilirubin (mg/dL). A DF score of > 32 in cases of hepatic encephalopathy predicts a > 50% chance of death within 28 d in alcoholic hepatitis patients. However, mortality has also been seen to occur in patients with a modified DF score of < 32, which suggests a need for alternative scoring systems due to the low specificity of the DF.

One reliable measure of the risk of mortality in patients with end-stage liver disease is The Model for End-Stage Liver Disease (MELD). A MELD score of  $\geq 21$  (within 24 h of presentation) is a good indication of a 90-d life expectancy. Both the MELD and modified DF scores (within 24 h of presentation) provide a similar prognosis in predicting 30- and 90-d life expectancy in AH patients<sup>[33]</sup>.

One composite scoring system based on age, blood urea nitrogen, serum bilirubin prothrombin time (PT), and peripheral leucocyte count is The Glasgow Alcoholic Hepatitis Score (GAHS). A GAHS score equal to or >

9 provides a prognosis of life expectancy and is more accurate than DF as a prediction of both 28- and 84-d mortality, but is similar to MELD in predicting the 28-d mortality.

Another model, The Lille, includes age, renal insufficiency, PT, albumin, and bilirubin and its evolution on day 7 in order to predict the 6-mo life expectancy in acute alcoholic hepatitis patients who have undergone corticosteroid therapy<sup>[33]</sup>.

The ABIC score, which takes into consideration age, serum bilirubin, INR, and the serum creatinine score, has been suggested as a standard for AH. Preliminary studies testing the ABIC score have suggested greater accuracy in predicting 28-d and 90-d outcomes than DF, but external validation is still needed (EASL)<sup>[34]</sup>.

In terms of pharmacology, along with lifestyle changes and adequate nutrition, there is evidence indicating the usefulness of glucocorticoids, pentoxifylline (a suppressor of TNF- $\alpha$ , thus preventing leukocyte adherence to vascular endothelium and reduces the incidence of intracellular adhesion of the molecule-1 in monocytes), infliximab (a chimeric antibody found in mice and human, which binds to the TNF- $\alpha$ ), S-adenosyl-methionine (a precursor to glutathione), antioxidants and colchicine.

A common trait in alcoholics is significant protein calorie malnutrition, as well as a lack of a variety of vitamins and minerals, the most common being vitamins A and D, thiamine, folate, pyridoxine, and zinc<sup>[1,4]</sup>.

Currently, the mainstay treatment for acute AAH is the provision of glucocorticoids. Despite this, the efficacy of corticosteroids is still regarded as being a debatable issue for some authors. A comprehensive review of the relevant literature was carried out which came to the conclusion that a more discerning use of glucocorticoids in patients with a DF score of  $\geq 32$  is required<sup>[35]</sup>. These authors recommend that glucocorticoids be withdrawn if there is no improvement in bilirubin after 7 d; changing over to pentoxifylline could be a reasonable alternative in these cases. Common contraindications are recent upper gastrointestinal bleeding, uncontrollable infection and renal failure.

A meta-analysis was carried out using the data from more than 200 patients with a modified DF equal to or more than 32<sup>[36]</sup>. They concluded that the 28-d survival rate with the use of glucocorticoids was 85%, while a placebo yielded a result of 65%. Patients with a modified DF equal to or > 32 improved in the short-term when treated with glucocorticoids in terms of a 28-d life expectancy, with the mortality rate falling from 35% in the control group to 15% in those treated with steroid therapy. On the other hand, patients with a modified DF of < 32 had a > 90% survival rate without the use of steroids. More recently, improved survival rates were demonstrated during a study researching the use of corticosteroid treatment<sup>[6]</sup>. In this study, those patients receiving corticosteroid treatment had higher 28-d survival rates than those receiving non-corticosteroid treatment. The results were 80% and 66%, respectively. The patients

were classified into three groups: the first consisted of complete responders (a Lille score of  $<$  or equal to 0.16;  $<$  or equal to the 35<sup>th</sup> percentile); the second group consisted of partial responders (a Lille score of 0.16-0.56; within the 35<sup>th</sup>-70<sup>th</sup> percentile); and the third group consisted of null responders (a Lille score of  $>$  or equal to 0.56;  $>$  or equal to the 70<sup>th</sup> percentile). This method identified three categories of response: complete, partial, and null, with significant differences in life expectancy (91%, 79% and 53%, respectively,  $P < 0.0001$ ). Corticosteroids had a significant effect on 28-d survival in the complete responder and in partial responder groups, but not in the null responder group.

The EASL emphasises the crucial role of nutrition. The recommended protein-caloric ingestion is often difficult by mouth in a significant percentage of AH patients. A randomised, controlled trial which compared intestinal nutrition with corticosteroids did not yield any difference in the 28-d life expectancy, although mortalities occurred sooner with intestinal nutrition, steroid therapy caused a higher mortality rate in the weeks following treatment. A combination of intestinal nutrition with corticosteroids should be tested<sup>[34]</sup>.

In ALD and AH, how to manage bleeding due to portal hypertension is similar to that in other causes of end-stage chronic liver disease. Hepatorenal syndrome (HRS) in spontaneous bacterial peritonitis can be avoided with oral pentoxifylline: this decreases the risk of HRS and of death from 35% and 46%, respectively (in control groups) to 8% and 24%, respectively. The AASLD and the American Gastroenterological Association have issued guidelines advising the prescription of pentoxifylline (400 mg orally 3 times a day for 4 wk) instead of glucocorticoids in patients with acute AH (DF  $>$  32), especially if there are adverse reactions to glucocorticoids<sup>[1,30,37]</sup>.

The placement of a transjugular intrahepatic portosystemic stent shunt (TIPS) in patients with AAH with HRS could keep portal hypertension under control and improve renal function with a significant decrease in serum creatinine levels along with an increased output of urine. In conclusion we can state that TIPS is a worthwhile option for patients with advanced alcoholic liver disease, or with acute AAH with complications caused by HRS, and who are waiting for an LT<sup>[38,41]</sup>.

One possible treatment option for acute AAH is LT, but these are rarely carried out due to the required 6-mo abstinence period before being allowed on the waiting list. LT should be considered as a necessary therapeutic option in patients with AAH, due to the high risk of early mortality.

In one study 26 patients were listed for transplantation (average age: 47.4 years), who had not responded to medical therapy after an average time of 13 d<sup>[42]</sup>. There was an average wait of 9 d for transplantation. A Lille score of 0.45 or more indicated a non-response to steroids or a significant deterioration of liver function. There was a much higher 6-mo survival rate in patients who had received transplantation (77%  $\pm$  8%) than in the

case-matched controls (23%  $\pm$  8%). During this period there were no observed alcoholic relapses, although three patients later started consuming alcohol again. None of the patients showed signs of graft dysfunction.

A further study demonstrated that the patients surviving AAH, as well as the post-LT recidivism rates produced the same statistical results as the overall group of those receiving transplantation<sup>[43]</sup>.

We observed seven patients with an average age of 49, who did respond not to medical therapies, and who manifested clinical evidence of acute AAH (MELD  $>$  21 and DF  $>$  32) and type-1 HRS. They were submitted to TIPS followed by successful transplantations after 30-45 d. They were advised against the use of steroids due to the risk of renal failure. During the first 5 years of follow-up, none of these patients went back to consuming alcohol<sup>[44,45]</sup>.

Recently it was shown that, when patients with alcoholic cirrhosis were compared with those with alcoholic hepatitis, they presented similar post-LT graft and survival rates<sup>[46]</sup>.

We can draw the conclusion from these initial findings that LT could be a significant treatment option in those patients with alcoholic hepatitis who do not improve with medical therapy.

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## PROPOSAL FOR ALCOHOL AND LIVER TRANSPLANTATION

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The EASL has reported that general practitioners most likely consider that alcoholic patients should be given lower priority than other patients, due to the lack of donor organs, even when the alcoholics had a lower chance of a successful result from transplantation<sup>[34]</sup>.

The results of liver transplantations for ALD are as successful as those for other reasons, whereas patients with HCV have lower patient and graft survival rates than those with ALD.

Reports by the Japanese Liver Transplantation Society indicate survival rates in ALD patients of 81.3% after 1 year, 78.5% after 3 years and 75.7% after 5 years. Similar results were reported in Europe for ALD patients of 84% after 1 year, 78% after 3 years and 73% after 5 years. In the United States the results were 92% after 1 year and 86% after both 3 and 5 years. Recently, another study recorded the long-term survival rates after living donor liver transplantation. The survival rates after 1, 3, and 5 years overall survival were 100%, 91% and 91% in a group with ALD, respectively, and 90%, 86% and 83% in a non-ALD group, respectively<sup>[7]</sup>.

There is insufficient scientific evidence which backs up the 6-mo sobriety rule in patients who have both progressive end stage liver disease (ESLD) and with AAH, and who do not respond to steroid therapy<sup>[8]</sup>.

ESLD patients who do not recover within the first 3 mo of abstinence generally die, indicating a 3-mo period of abstinence could be more useful than a 6-mo period<sup>[47]</sup>.

For patients with AAH, up to 70% of whom die



**Table 1 Risk factors for predicting alcohol relapse**

Alcohol drinking anamnesis (consumption habits: harmful drinking or mild/moderate dependence)
Drug abuse anamnesis
Family history of alcohol abuse/dependence
Psychiatric comorbidities
High risk alcoholism relapse test, SCL 90 Score
Adherence to treatment: patients are asked to attend follow-up appointments
Ability to develop a therapeutic alliance, and to build good relationships with the transplant team
Social support (family, friends)
Self-help group attendance and active participation
Adherence to behavioural support programs
Alcohol units attendance, with the presence of an addiction specialist/hepato-alcoholologist
Period of abstinence before liver transplantation

within 6 mo, LT should be compulsory for some, even if these patients did not abstain<sup>[42]</sup>.

The UNOS and the French Consensus Conference<sup>[48]</sup> have confirmed that: (1) A 6-mo abstinence period should not be compulsory for patients with progressive ESLD and/or AAH, and who do not respond to steroid therapy, nor should it be a determining factor for graft access; (2) the word “recurrence” does not seem correct: it would be better use the term “relapse” in alcoholics to differentiate it from isolated cases of alcohol consumption; (3) the term “relapse” should not always be used to describe one episode of alcohol consumption; (4) alcoholic cirrhosis is still a good indication of LT; the success and failure rates are similar to LTs for non-alcoholic causes of cirrhosis; (5) LT for alcoholic cirrhosis should be the cornerstone of treating alcoholic patients, thus giving specific responsibilities to the medical staff involved in their follow-up care. There should be a system in place for the management of alcohol-related diseases by specialised teams. Therefore, a team which specialises in alcoholic-related problems is recommended; and (6) there must be a change in social attitudes towards alcoholic patients. These patients should be seen as suffering from a double pathology, both hepatic and alcoholic.

Studies concerning alcoholism are used to label any alcohol intake as a “relapse”. This statement is under debate, and some further clarifications are needed. Indeed, relapse may be defined as the resumption of heavy alcohol intake.

Approximately 10% of patients relapse into heavy drinking usually within the first year after liver transplantation, as confirmed by the EASL<sup>[34]</sup>.

Furthermore, it has been indicated that a relapse into consuming alcohol shows risk of alcoholism, but not always of ALD<sup>[49]</sup>. This disassociation could be due to the fact that a transplanted liver changes the patient’s genetic tendency towards damage by alcohol. There have been challenges to this focus on alcoholic relapse, rather than survival being the primary result after transplantation for alcoholic cirrhosis.

Another report showed that the rates of alcohol re-

lapse ranged from 11.5% to 49%, although this was rarely a consideration when looking for reasons for graft failure in ALD patients<sup>[50]</sup>. Relapse directly leading to graft dysfunction ranged from 0% to 17%, whereas relapse directly causing mortality ranged from 0% to 5%.

It has been successfully affirmed that 3 mo of abstaining from consuming alcohol may be more useful than 6 mo<sup>[51]</sup>. There are other groups of patients who should only be included with caution: patients with a lack of social support, those who smoke, those with psychotic or personality disorders, or those with a pattern of relapse.

We are not sure if this is an effective indicator for post-transplant abstinence, or just a consistent method of selection, approved by insurance companies<sup>[52]</sup>.

Although there is evidence that a shorter pre-listing abstinence period corresponds to a shorter period before post-transplant relapse, the ideal period of abstinence pre-transplant is still debatable<sup>[52]</sup>.

Therefore, other factors must be identified that are associated with a relapse into drinking alcohol (Table 1).

A multivariate logistic regression analysis was carried out on dangerous drinking post-transplantation and found the following: an abstinence period of under 6 mo, patients with psychiatric disorders, and patients with a high risk alcoholism relapse score of higher than 3 all significantly corresponded to an increased incidence of relapse<sup>[53]</sup>. In patients who had none of these 3 factors, alcohol relapse was 5%, while the presence of 1, 2, or 3 of the factors corresponded to relapse rates of 18%, 64%, and 100%, respectively. Therefore, they declared that the overall survival rate seems not to be significantly affected by alcohol relapse.

It is well-known, in fact, that the leading causes of death post-LT are: cancer, cardiac diseases and infections<sup>[19,53]</sup>.

It has been emphasised that teenage patients who suffer liver failure after a deliberate paracetamol overdose, after consuming ecstasy, or after contracting hepatitis B through irresponsible sexual practice should have full access to LT<sup>[54]</sup>. There is no reason why their peers with alcoholic hepatitis should be treated differently.

There is a risk that the 6-mo rule may be used as an excuse for not having to make difficult ethical decisions<sup>[54]</sup>.

Specialised Alcohol Units (AU) responsible for the early management of ALD patients could play a significant role in their long-term prognosis.

Altamirano *et al.*<sup>[55]</sup> reported a median of 40 mo between ALD diagnosis and the first medical examination in a specialized alcohol unit (AU). This fact necessarily leads to a growing public health concern: a proper national action plan is urgently required to encourage patients to turn to specialized AU in the early stage of the disease, and before liver transplant is needed.

The policy of the strict application of an abstinence period in order to be eligible for transplant is not fair on acute AAH and/or ESLD patients, as most of them die before the end of the 6-mo period.

Most ESLD patients usually do not recover even during the first 3 mo of sobriety, and acute AAH pa-

tients usually die. Therefore, a shorter period before LT would be more appropriate. Patients who have good social support, who do not suffer from psychotic or personality disorders, and who have decompensated liver disease, should be added to the liver transplant list, without taking the length of their period of abstinence into consideration<sup>[44,45]</sup>.

One study confirmed that when patients relapse, the risk of developing graft loss or ALD is not easy to predict as the transplanted liver changes their genetic tendency alcoholic damage<sup>[56]</sup>. They concluded that the period of abstinence pre-LT should be less, at least in patients who are strictly controlled by an Alcohol Addiction Unit.

There should be compulsory pre- and post-LT self-help group attendance and active participation (for example, Alcoholics Anonymous)<sup>[44,57]</sup>.

Post-LT patients with other minor medical conditions and who have strong social support, should be offered cognitive behavioural therapy, while patients with significant other medical conditions and/or limited social support should be allowed onto multi-component programs, which include multi-dimensional family therapy, functional family therapy and brief strategic family therapy<sup>[45,58]</sup>.

In conclusion, we consider that patients with progressive ESLD and acute AAH, and who do not respond to medical treatment, should not be excluded from liver transplant waiting lists solely due to a lack of pre-LT abstinence<sup>[51]</sup>.

Alcoholism is a disease; it should not be considered a reason to exclude patients from being listed for LT.

Public education campaigns are strongly needed; alcoholism should be universally recognised as a disease, and LT as a possible therapeutic option to treat patients and to save lives<sup>[59-64]</sup>.

The “Group of Italian Regions” (Department of Health), on the basis of a comprehensive review of the published literature, and, with particular regard to the daily clinical practice of those who have participated in the workshop “Alcohol and Liver Transplant”, affirms that the “6-mo rule” is not an evidence-based practice<sup>[65]</sup>.

Therefore the “Group of Italian Regions” suggests the following: (1) screening of de novo tumors after liver transplantation, and prevention of cardiovascular complications are needed to achieve better long-term outcomes; (2) Child-Pugh class “C” cirrhotic patients with ESLD should be placed on the transplant list; (3) in cases of ESLD with MELD < 19 six months of abstinence are required; (4) in cases of progressive ESLD with MELD > 19, three months of abstinence are more ideal than six months in selected patients; (5) in cases of severe AAH, not responding to medical therapy (Maddrey DF > 32 or MELD > 21), LT is mandatory in selected patients, independent of the sober period achieved; (6) the multidisciplinary transplant team must include an addiction specialist/hepato-alcoholologist; and (7) patients have to participate in self-help groups.

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