

# Treatment of Alcoholic Liver Disease

**Christopher Paul Day**

*Institute of Cellular Medicine, The Medical School, Newcastle University, United Kingdom*

## KEY CONCEPTS

Severe alcoholic steatohepatitis (ASH) is the major complication of advanced alcoholic liver disease (ALD) and has a high mortality even when treated with corticosteroids.

Despite the importance of reactive oxygen species in the pathophysiology of ALD and ASH, antioxidants provide no benefit in the treatment of patients with ASH.

Proinflammatory cytokines are important in the pathophysiology of ALD and might mediate most of the inflammatory aspects of these disorders.

New treatment modalities in ASH might involve antagonism of proinflammatory cytokines such as tumor necrosis factor (TNF) by specific antibodies or other TNF-interfering treatment strategies. Propylthiouracil and S-adenosyl methionine may be beneficial to patients with alcoholic cirrhosis, but both require further randomized, controlled trials before their use can be recommended.

Liver transplantation is an effective therapy for patients with advanced alcoholic cirrhosis who have not recovered after a period of abstinence. *Liver Transpl* 13: S69-S75, 2007. © 2007 AASLD.

Chronic consumption of alcohol can cause a spectrum of liver abnormalities, ranging from simple steatosis (fatty liver) to steatohepatitis, cirrhosis, and hepatocellular carcinoma. Patients with alcohol-related steatosis rarely manifest symptoms or signs suggestive of liver disease and are usually identified incidentally from abnormal blood test results. Although steatosis can reverse within a few weeks of sobriety,<sup>1</sup> it is a risk factor for progression to fibrosis and cirrhosis in patients who continue drinking, particularly when the steatosis is severe. Only a minority of consistent, heavy drinkers with hepatic steatosis will develop clinically relevant liver disease, which suggests that other host or envi-

ronmental factors are important in determining the evolution of alcohol-related liver disease.<sup>2</sup>

Risk factors for serious liver damage in habitual alcohol drinkers include polymorphisms in genes encoding alcohol-metabolizing enzymes, genetic hemochromatosis, female sex, infection with hepatitis C virus, obesity, exposure to other hepatotoxins (e.g., acetaminophen), smoking, and absence of coffee drinking.<sup>2</sup> In most patients, however, an additional causative factor is never identified. Common clinical presentations of alcoholic liver disease (ALD) are the syndrome of acute alcoholic steatohepatitis (ASH) and/or cirrhosis and its complications. This paper focuses on the current management of patients with ALD, with emphasis on ASH and liver cirrhosis

## ABSTINENCE: THE CORNERSTONE OF THERAPY

Because the cessation of alcohol or a marked reduction in alcohol intake improves histology and/or survival of patients with any stage of ALD,<sup>3</sup> alcohol abstinence is the cornerstone of management for patients with ALD. However, no formal trials have been conducted of either psychological or pharmacological therapies aimed at reducing alcohol intake specifically in patients with ALD.

## ASH

### Prognosis

The severity of ASH correlates with the serum bilirubin level and prothrombin time (PT) after vitamin K administration. As part of a seminal clinical study on corticosteroid therapy in severe ASH, the discriminant function (DF) formula (bilirubin [mg/dL] + 4.6 [PT prolongation]) was derived to predict disease severity

**Abbreviations:** ALD, alcoholic liver disease; ASH, alcoholic steatohepatitis; PT, prothrombin time; DF, discriminant function; MELD, Model for End-stage Liver Disease; GAHS, Glasgow Alcoholic Hepatitis Score; PTX, pentoxifylline; TNF, tumor necrosis factor; LT, liver transplantation.

Address reprint requests to Christopher Paul Day, Institute of Cellular Medicine, Newcastle University, Floor 4 William Leeds Building Medical School, Framington Place, Newcastle upon Tyne NE2 4HH UK. Telephone: +44 191 222 7043; FAX: +44 191 222 0723.

DOI 10.1002/lt.21336

Published online in Wiley InterScience (www.interscience.wiley.com).

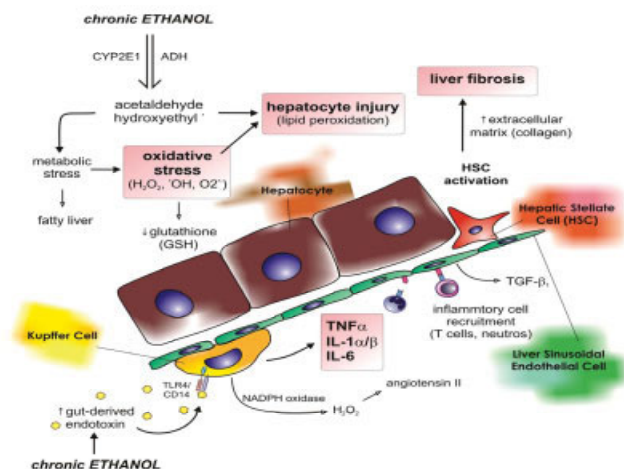
	1	2	3
Age	< 50	≥ 50	-
WCC (10 <sup>9</sup> /l)	< 15	≥ 15	-
Urea (mmol/l)	< 5	≥ 5	-
PT ratio	< 1.5	1.5 – 2.0	> 2.0
Bilirubin (μmol/l)	< 125	125 - 250	> 250

**Figure 1. Glasgow Alcoholic Hepatitis Score (GAHS).** PT, prothrombin time; WCC, white cell count. From Forrest EH, Evans CD, Stewart S, Phillips M, Oo YH, McAvoyn NC, et al. Analysis of factors predictive of mortality in alcoholic hepatitis and derivation and validation of the Glasgow Alcoholic Hepatitis Score. *Gut* 2005;54:1174-1179.

and individual mortality risk in these patients.<sup>4</sup> This DF was later modified in the context of a further placebo-controlled corticosteroid trial. A modified discriminant function of >32 and/or the presence of encephalopathy in placebo-treated patients in this latter study was associated with a 65% 28-day survival.<sup>5</sup> A reanalysis has since confirmed this finding and has also demonstrated that patients with a score of <32 had a survival of 93%.<sup>6</sup> A cutoff value of 32 has therefore been used and is recommended as the threshold to consider corticosteroid treatment.<sup>7</sup> The Model for End-stage Liver Disease (MELD) score has also been used as a prognostic parameter in ASH,<sup>8</sup> and Forrest et al.<sup>9</sup> have recently developed a new score for ASH—the Glasgow Alcoholic Hepatitis Score (GAHS) (Fig. 1). Factors included in the GAHS are age, white blood cell count, blood urea nitrogen concentration, PT ratio, and serum bilirubin concentration. The superiority of MELD and GAHS to the modified DF in predicting short-term and long-term survival awaits further studies.

### Pharmacological Therapy

Progress in developing specific treatments for acute ASH has been limited by poor understanding of disease pathogenesis. Animal models indicate that ASH occurs as a result of oxidative stress and/or endotoxin-mediated cytokine release, which act through leukocyte recruitment and activation to cause hepatocyte dysfunction, apoptosis, and necrosis (Fig. 2). At present, however, evidence for these mechanisms in humans is at best indirect. As a reflection of the lack of understanding of the pathophysiology of ASH, many treatment modalities have been tried in patients with ASH; however, none has been consistently shown to have a beneficial effect, and accordingly, none has achieved consensus status among practicing hepatologists.



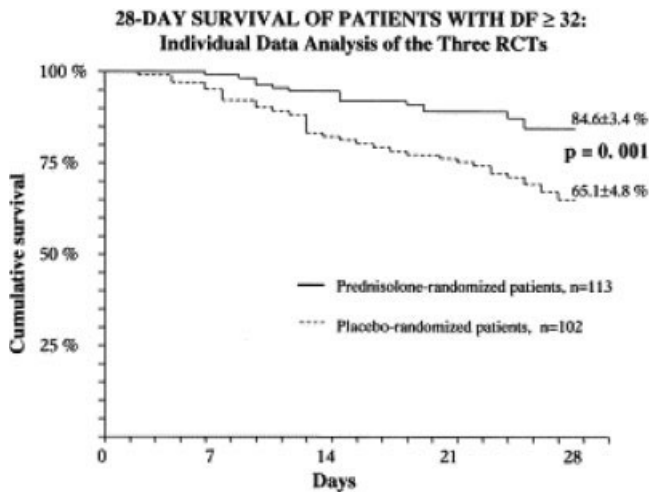
**Figure 2. Current view of pathogenesis of alcohol-induced liver inflammation and role of the innate immune system.** ADH, alcohol dehydrogenase; CYP2E1, cytochrome P-450 2E1; TLR, toll-like receptor; TNF, tumor necrosis factor; IL, interleukin. From Tilg H, Day CP. Management strategies in alcoholic liver disease. *Nat Clin Pract Gastroenterol Hepatol* 2007;4:24-34.

### Corticosteroids

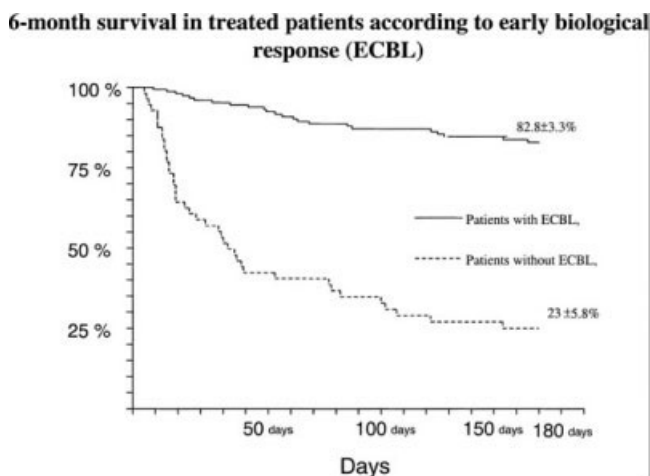
Of all the treatments available for patients with severe ASH, corticosteroids have been studied most intensively. Many initial corticosteroid trials were poorly designed and included patients who most likely did not have ASH. Most of these trials showed no treatment benefit; however, 2 randomized, controlled trials focusing only on patients who had the worst prognosis (defined by a DF of >32 and/or encephalopathy)<sup>5,10</sup> showed a survival benefit of corticosteroid use. The authors of the last 3 large randomized, controlled trials pooled their individual patient data and included only patients with encephalopathy and/or a DF of >32 (Fig. 3).<sup>6</sup> This study showed that corticosteroids improved survival vs. placebo (85% vs. 65%). A change in circulating bilirubin levels on day 7 of therapy (i.e., a bilirubin level lower than the level on the first day of treatment) might be another important prognostic factor favoring a clinical response to corticosteroid therapy (Fig. 4).<sup>11</sup> The survival benefit from corticosteroid therapy persists for only 1 year.<sup>12</sup>

### Antioxidants

Interest in the potential value of antioxidant therapy as a treatment for ASH derives from the growing body of evidence suggesting that oxidative stress is a key mechanism underlying alcohol-mediated hepatotoxicity (Fig. 2). In the most recent study, corticosteroids were compared with an antioxidant cocktail ( $\beta$ -carotene, vitamins C and E, selenium, methionine, allopurinol, desferrioxamine, and N-acetylcysteine); corticosteroid treatment had better efficacy and a higher survival rate (Fig. 5).<sup>13</sup> The survival advantage for the corticosteroid-treated patients, however, was lost at 1 year of follow-up. Another study investigated the role of antioxidants



**Figure 3. Twenty-eight-day survival in patients with discriminant function  $>32$  treated with corticosteroids or placebo.** From Mathurin P, Mendenhall CL, Carithers RL Jr, Raymond MJ, Maddrey WC, Garstide P, et al. *Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis AH: Individual data analysis of the last three randomized placebo controlled double blind trials of corticosteroids in severe AH.* *J Hepatol* 2002;36:480-487.

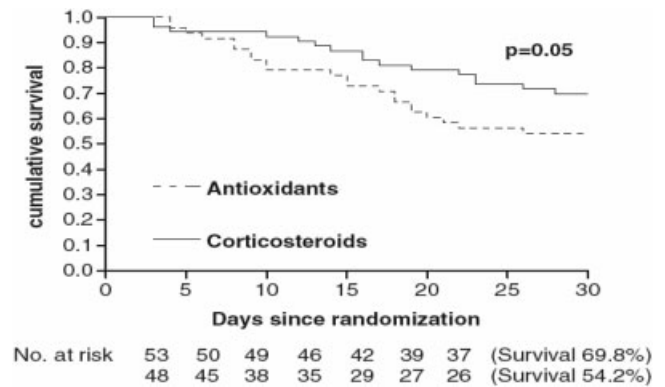


**Figure 4. Six-month survival in patients treated with corticosteroids according to early biological response (ECBL).** From Mathurin P, Abdelnour M, Ramond MJ, Carbonell N, Fartoux L, Serfaty L, et al. *Early change in bilirubin levels is an important prognostic factor in severe alcoholic hepatitis treated with prednisolone.* *Hepatology* 2003;38:1363-1369.

in patients with severe ASH who were stratified by gender and corticosteroid treatment.<sup>14</sup> The active group received an initial loading dose of N-acetylcysteine of 150 mg/kg followed by 100 mg/kg/d for 1 week, and vitamins A and E, biotin, selenium, zinc, manganese, copper, magnesium, folic acid, and coenzyme Q daily for 6 months. Antioxidant therapy showed no benefit either alone or in combination with corticosteroids.

#### Nutritional Supplements

The efficacy of nutritional therapy in ASH has been evaluated in numerous clinical trials. Although results



**Figure 5. Randomized, controlled trial of antioxidants vs. corticosteroids.** From Phillips M, Curtis H, Portmann B, Donaldson N, Bomford A, O'Grady J. *Antioxidants versus corticosteroids in the treatment of severe alcoholic hepatitis—a randomised clinical trial.* *J Hepatol* 2006;44:784-790.

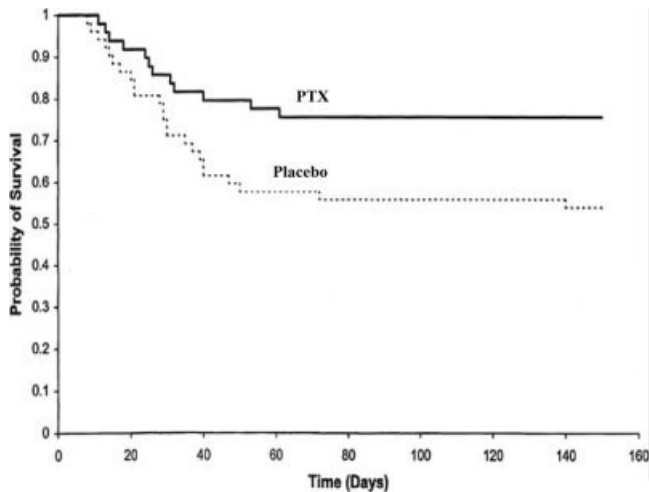
have varied, most studies have shown that nutritional therapy improves liver function and histology with no consistent reduction in mortality. A recent study has compared enteral feeding with corticosteroids in 71 patients with acute severe ASH.<sup>15</sup> Although there was no difference in mortality between the groups during the 28-day treatment period, deaths occurred earlier in the corticosteroid-treated patients, and the mortality rate was lower in the enterally fed group in the year after treatment.

#### Pentoxifylline

Pentoxifylline (PTX) is a nonselective phosphodiesterase inhibitor that has a moderate anticytokine effect attributed to reduced transcription of the tumor necrosis factor (TNF) gene. In the first randomized, controlled trial of PTX in patients with ASH, PTX was provided for 28 days to 101 patients who had a DF of  $>32$  and led to a 40% reduction in mortality compared with placebo (Fig. 6).<sup>16</sup> Importantly, almost all of the improvement in survival was due to a decrease in mortality from hepatorenal syndrome. Further trials are needed to determine whether PTX should become a standard treatment for patients with ASH.

#### Anti-TNF Antibody Treatment

The belief that TNF plays a role in the pathogenesis of ALD (Fig. 2) has led to several studies with the anti-TNF antibody infliximab (Remicade) in patients with ASH. This chimeric human and mouse monoclonal antibody binds to TNF and blocks its biological effects. The first study randomly allocated 20 patients with biopsy-proven severe ASH to prednisone 40 mg/d for 28 days plus either infliximab 5 mg/kg (single dose) or placebo.<sup>17</sup> At day 28, DF improved greatly only in the prednisone plus infliximab group. Liver histology findings were improved after a median time of 10 days (range, 8-12 days). A further pilot study treated 12 patients with biopsy-confirmed ASH and a DF of  $>32$  with infliximab alone (single dose, 5 mg/kg) and reported a marked decrease in bilirubin levels, DF, neutrophil

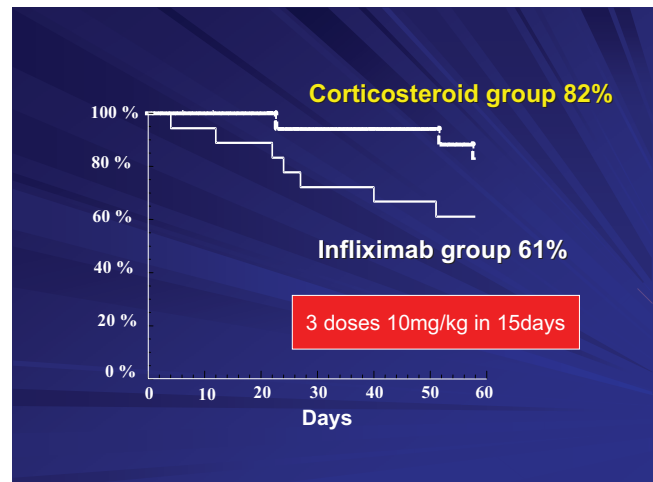


**Figure 6. Randomized, controlled trial of pentoxifylline vs. placebo.** From Akriavidis E, Botla R, Briggs W, Han S, Reynolds T, Shakil O. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000;119:1637-1648.

counts, C-reactive protein, and reduced liver fat content and neutrophil infiltration.<sup>18</sup> Mookerjee et al.<sup>19</sup> tested the hypothesis that TNF is an important mediator of circulatory disturbances in ASH in infliximab-treated patients. The mean hepatic venous pressure gradient decreased greatly at 24 hours after administration of infliximab with a sustained reduction before hospital discharge. A small French multicenter randomized, controlled trial studying infliximab in 36 patients with ASH was stopped in October 2002 by the French drug agency because of increased mortality in the infliximab group (Fig. 7).<sup>20</sup> In this study, the authors compared prednisolone (40 mg/d) with either placebo or infliximab given intravenously (10 mg/kg 3 times, at weeks 0, 2, and 4). The mean end point was 2 months' mortality after the initial dose. An interim analysis revealed an increase in the incidence of infection and higher mortality in the infliximab group, although this increase did not reach statistical significance.

### Liver Transplantation for ASH

Most clinical centers do not consider patients with severe acute ASH for liver transplantation (LT). Nonetheless, there have been isolated reports of survival after transplantation of patients with severe acute ASH. In addition, there has been a report that the presence of histological alcoholic hepatitis in the explanted liver of patients transplanted for apparently chronic stable ALD is not associated with a worse prognosis or an increased risk of recidivism.<sup>21</sup> Clearly, some patients with ASH can benefit from transplantation. However, more data are required before any firm recommendations can be provided on which patients (if any) are likely to derive the most benefit.



**Figure 7. Randomized, controlled trial of infliximab (Remicade) vs. corticosteroids.** From Naveau S, Chollet-Martin S, Dharancy S, Mathurin P, Jouet P, Piquet MA, et al, for the Foie-Alcool group of the Association Française pour l'Etude du Foie. A double-blind randomized controlled trial of infliximab associated with prednisolone in acute alcoholic hepatitis. *Hepatology* 2004;39:1390-1397.

### ALCOHOLIC LIVER CIRRHOSIS

Although the high mortality of severe ASH, coupled with the young age of many of the patients, makes it an important area for therapeutic trials, most patients with ALD in clinical practice have advanced fibrosis or cirrhosis. The most important therapy is achieving and maintaining abstinence, because this has been shown to improve survival in patients with well-compensated or decompensated liver disease.<sup>3</sup> Unfortunately, no adjunctive pharmacotherapies have been shown to improve survival in more than one randomized, controlled trial, although some have shown promise. As a result, the management of patients with advanced ALD is currently directed primarily at preventing and treating the complications of cirrhosis and deciding if and when to consider patients for orthotopic LT.

#### Pharmacological Therapy

##### *Propylthiouracil*

There has been one trial of propylthiouracil in alcoholic liver cirrhosis reported to date in which treatment for 2 years improved mortality, particularly in patients who continued to drink moderately during the trial.<sup>22</sup> Although the patient numbers were high ( $n = 310$ ), a large percentage of patients were either noncompliant or dropped out of the study. For this reason, and as a result of the lack of any confirmatory studies, propylthiouracil has not been adopted as a treatment for alcoholic liver cirrhosis.

##### *Colchicine*

Colchicine is an antiinflammatory drug that has been evaluated in the treatment of patients with alcohol-related and non-alcohol-related cirrhosis because of its antifibrotic effect *in vitro*. However, a metaanalysis of

14 randomized, controlled trials of colchicine has found no benefit of colchicine treatment on mortality or liver histology in cirrhosis, and this has been confirmed by a further large randomized study.<sup>23,24</sup>

### Antioxidants

The evidence that oxidant stress is involved in the pathogenesis of ALD has prompted trials of antioxidants in patients with alcoholic liver cirrhosis. Two trials have evaluated the drug silymarin, which is the active component of the herb milk thistle and has potent antioxidant properties in vitro and in vivo. The first trial in 170 patients with cirrhosis (92 had ALD) who were followed up for 2-6 years reported a beneficial effect of silymarin on survival.<sup>25</sup> By contrast, a later, larger study of 200 patients with cirrhotic ALD who were followed for 5 years showed no survival benefit.<sup>26</sup> S-adenosyl methionine, which acts both as an antioxidant by replenishing glutathione levels and as a methyl donor maintaining cell membrane fluidity, has also been evaluated in patients with alcoholic cirrhosis. With death or LT used as a combined end point, Mato et al.<sup>27</sup> reported a beneficial effect of S-adenosyl methionine treatment in patients with Child-Pugh class A and B cirrhosis. Further trials with this agent are awaited with interest.

### Phosphatidylcholine

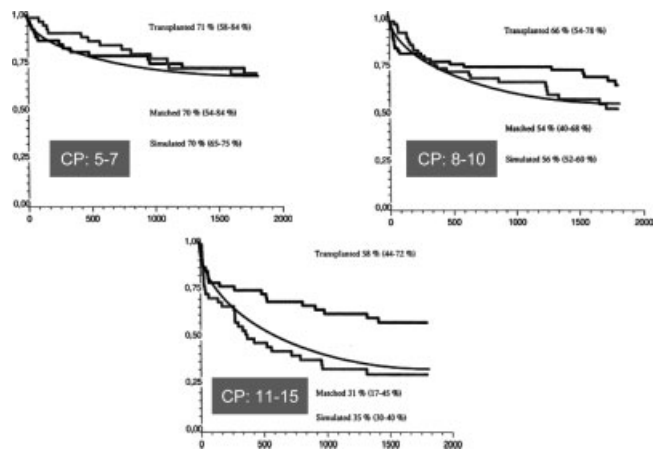
Phosphatidylcholine is an essential component of all cell membranes and is vulnerable to attack by lipid peroxidation. Through mechanisms that are as yet unclear, dietary supplementation with phosphatidylcholine has been shown to attenuate ethanol-induced fibrosis in baboons. In a long-term trial in patients with alcoholic cirrhosis, there was a trend toward improvement in transaminase and bilirubin levels in the phosphatidylcholine group for certain patient subgroups (heavy drinkers and those with hepatitis C), but there was no overall improvement in mortality or liver histology at 24 months.<sup>28</sup>

## LT FOR ALCOHOLIC CIRRHOSIS

LT for patients with ALD remains controversial, principally as a result of concerns about the risk of posttransplantation relapse and its effect on outcome and public opinion at a time of increasing donor shortage. These issues, coupled with a perception that these patients are more likely to have contraindications to transplantation, either as a result of extrahepatic complications of excessive alcohol abuse or an associated lack of self-care, have contributed to a continued reluctance of many centers to offer LT to patients with ALD.

### Outcome of LT for ALD

Several studies have demonstrated that the survival of patients who undergo transplantation for cirrhotic ALD is comparable to patients with cirrhosis of alternative etiologies, with 5- and 10-year survival rates lying somewhere between those of patients transplanted for cholestatic and viral hepatitis-related liver disease.



**Figure 8. Survival of alcoholic liver disease patients transplanted vs. nontransplanted and simulated controls by Child-Pugh (CP) score. From Poynard T, Barthelemy P, Fratte S, Boudjema K, Doffoel M, Vanlemmens C, et al. Evaluation of efficacy of liver transplantation in alcoholic cirrhosis by a case-control study and simulated controls. *Lancet* 1994;344:502-507.**

Furthermore, there is no evidence that patients with ALD have a higher frequency of postoperative complications or resource use compared with patients transplanted for other indications, despite undergoing transplantation at a more advanced stage of disease.<sup>29</sup> Poynard et al.<sup>30</sup> demonstrated that ALD patients with severe disease, as judged by a Child-Pugh score of  $\geq 11$ , had a greatly improved 5-year survival with transplantation compared with matched and simulated controls, whereas patients with less severe liver disease fared no better with transplantation (Fig. 8).

### Posttransplantation Relapse

Perhaps the greatest concern when considering transplantation for patients with ALD is the risk of relapse and its effect on outcome and public opinion. Efforts to minimize the risk of posttransplantation relapse are therefore important, not only for the individual patient, but also to avoid the likely adverse effect this has on the organ-donating public.

### Comorbidity

Excessive alcohol consumption can affect many organ systems apart from the liver, and this can potentially give rise to contraindications to surgery. In practice, however, although many transplant units routinely screen ALD patients for cardiac and cerebral complications of excessive alcohol intake, this results in the exclusion of very few patients.<sup>31</sup>

### Preoperative Abstinence

Most centers require ALD patients to have been abstinent for a period of time before assessment. This is primarily to give the liver a chance to recover spontaneously, but it also allows time for other alcohol-related

morbidities to recover, thereby improving the patient's fitness for surgery and, importantly, satisfying public opinion. The role of preoperative abstinence in predicting posttransplantation recidivism remains controversial. Although there is broad consensus on the need for a period of pretransplantation abstinence, there is far less agreement on the requirement for a minimum duration. Many units have insisted on a 6-month period of abstinence, although a study that demonstrated that the chance of recovery in patients with decompensated ALD can be predicted as early as 3 months<sup>32</sup> has led some observers to suggest that, if required at all, the minimum period of abstinence could safely be reduced to 3 months rather than 6 months.<sup>33</sup> Currently, it seems that in practice most centers do not adhere strictly to a fixed period of abstinence, instead preferring to assess each case on an individual basis and listing the patient when it recovery is considered unlikely.<sup>34</sup>

## REFERENCES

- Lieber CS, Jones DP, DeCarli LM. Effects of prolonged ethanol intake: production of fatty liver despite adequate diets. *J Clin Invest* 1965;44:1009-1021.
- De Alwis NMW, Day CP. Genetics of alcoholic liver disease and nonalcoholic fatty liver disease. *Semin Liver Dis* 2007; 27:44-54.
- Powell WJ Jr, Klatskin G. Duration of survival in patients with Laennec's cirrhosis. Influence of alcohol withdrawal, and possible effects of recent changes in general management of the disease. *Am J Med* 1968;44:406-420.
- Maddrey WC, Boitnott JK, Bedine MS, Weber FL Jr, Mezey E, White RI Jr. Corticosteroid therapy of alcoholic hepatitis. *Gastroenterology* 1978;75:193-199.
- Carithers RL Jr, Herlong HF, Diehl AM, Shaw EW, Combes B, Fallon HJ, et al. Methylprednisolone therapy in patients with severe alcoholic hepatitis. A randomized multicenter trial. *Ann Intern Med* 1989;110:685-690.
- Mathurin P, Mendenhall CL, Carithers RL Jr, Ramond MJ, Maddrey WC, Garstide P, et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis (AH): individual data analysis of the last three randomized placebo controlled double blind trials of corticosteroids in severe AH. *J Hepatol* 2002;36:480-487.
- McCullough AJ, O'Connor JF. Alcoholic liver disease: proposed recommendations for the American College of Gastroenterology. *Am J Gastroenterol* 1998;93:2022-2036.
- Dunn W, Jamil LH, Brown LS, Wiesner RH, Kim WR, Menon KV, et al. MELD accurately predicts mortality in patients with alcoholic hepatitis. *Hepatology* 2005;41:353-358.
- Forrest EH, Evans CD, Stewart S, Phillips M, Oo YH, McAvoy NC, et al. Analysis of factors predictive of mortality in alcoholic hepatitis and derivation and validation of the Glasgow Alcoholic Hepatitis Score. *Gut* 2005;54:1174-1179.
- Ramond MJ, Poynard T, Rueff B, Mathurin P, Theodore C, Chaput JC, et al. A randomized trial of prednisolone in patients with severe alcoholic hepatitis. *N Engl J Med* 1992;326:507-512.
- Mathurin P, Abdelnour M, Ramond MJ, Carbonell N, Fartoux L, Serfaty L, et al. Early change in bilirubin levels is an important prognostic factor in severe alcoholic hepatitis treated with prednisolone. *Hepatology* 2003;38:1363-1369.
- Mathurin P, Duchatelle V, Ramond MJ, Degott C, Bedossa P, Erlinger S, et al. Survival and prognostic factors in patients with severe alcoholic hepatitis treated with prednisolone. *Gastroenterology* 1996;110:1847-1853.
- Phillips M, Curtis H, Portmann B, Donaldson N, Bomford A, O'Grady J. Antioxidants versus corticosteroids in the treatment of severe alcoholic hepatitis—a randomised clinical trial. *J Hepatol* 2006;44:784-790.
- Stewart S, Prince M, Bassendine M, Hudson M, James O, Jones D, et al. A randomized trial of antioxidant therapy alone or with corticosteroids in acute alcoholic hepatitis. *J Hepatol* 2007;47:277-283.
- Cabr e E, Rodr guez-Iglesias P, Caballer a J, Quer JC, S nchez-Lombr a JL, Par s A, et al. Short- and long-term outcome of severe alcohol-induced hepatitis treated with steroids or enteral nutrition: a multicenter randomized trial. *Hepatology* 2000;32:36-42.
- Akriviadis E, Botla R, Briggs W, Han S, Reynolds T, Shakil O. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000;119:1637-1648.
- Spahr L, Rubbia-Brandt L, Frassard J-L, Giostra E, Rougemont A-L, Pugin J, et al. Combination of steroids with infliximab or placebo in severe alcoholic hepatitis: a randomized controlled pilot study. *J Hepatol* 2000;37:448-455.
- Tilg H, Jalan R, Kaser A, Davies NA, Offner FA, Hodges SJ, et al. Anti-tumor necrosis factor-alpha monoclonal antibody therapy in severe alcoholic hepatitis. *J Hepatol* 2003; 38:419-425.
- Mookerjee RP, Sen S, Davies NA, Hodges SJ, Williams R, Jalan R. Tumour necrosis factor alpha is an important mediator of portal and systemic haemodynamic derangements in alcoholic hepatitis. *Gut* 2003;52:1182-1187.
- Naveau S, Chollet-Martin S, Dharancy S, Mathurin P, Jouet P, Piquet MA, et al, for the Foie-Alcool group of the Association Fran aise pour l'Etude du Foie. A double-blind randomized controlled trial of infliximab associated with prednisolone in acute alcoholic hepatitis. *Hepatology* 2004;39:1390-1397.
- Tom  S, Martinez-Rey C, Gonz lez-Quintela A, Gude F, Brage A, et al. Influence of superimposed alcoholic hepatitis on the outcome of liver transplantation for end-stage alcoholic liver disease. *J Hepatol* 2002;36:793-798.
- Orrego H, Blake JE, Blendis LM, Compton KV, Israel Y. Long-term treatment of alcoholic liver disease with propylthiouracil. *N Engl J Med* 1987;317:1421-1427.
- Rambaldi A, Gluud C. Colchicine for alcoholic and non-alcoholic liver fibrosis and cirrhosis [review]. *Cochrane Database Syst Rev*. 2005;(2):CD002148.
- Morgan TR, Weiss DG, Nemchausky B, Schiff ER, Anand B, Simon F, et al. Colchicine treatment of alcoholic cirrhosis: a randomized, placebo-controlled clinical trial of patient survival. *Gastroenterology* 2005;128:882-890.
- Ferenci P, Dragosics B, Dittrich H, Frank H, Benda L, Lochs H, et al. Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. *J Hepatol* 1989;9:105-113.
- Par s A, Planas R, Torres M, Caballer a J, Viver JM, Acero D, et al. Effects of silymarin in alcoholic patients with cirrhosis of the liver: results of a controlled, double-blind, randomized and multicenter trial. *J Hepatol* 1998;28:615-621.
- Mato JM, C mara J, Fern ndez de Paz J, Caballer a L, Coll S, Caballero A, et al. S-adenosylmethionine in alcoholic liver cirrhosis: a randomized, placebo-controlled, double-blind, multicenter clinical trial. *J Hepatol* 1999;30:1081-1089.
- Lieber CS, Weiss DG, Groszmann R, Paronetto F, Schenker S, for the Veterans Affairs Cooperative Study 391 Group. II. Veterans Affairs Cooperative Study of poly-enylphosphatidylcholine in alcoholic liver disease. *Alcohol Clin Exp Res* 2003;27:1765-1772.
- Wiesner RH, Lombardero M, Lake JR, Everhart J, Detre KM. Liver transplantation for end-stage alcoholic liver

- 
- disease: an assessment of outcomes. *Liver Transpl Surg* 1997;3:231-239.
30. Poynard T, Barthelemy P, Fratte S, Boudjema K, Doffoel M, Vanlemmens C, et al. Evaluation of efficacy of liver transplantation in alcoholic cirrhosis by a case-control study and simulated controls. *Lancet* 1994;344:502-507.
  31. Anand AC, Ferraz-Neto BH, Nightingale P, Mirza DF, White AC, McMaster P, et al. Liver transplantation for alcoholic liver disease: evaluation of a selection protocol. *Hepatology* 1997;25:1478-1484.
  32. Veldt BJ, Lainé F, Guillygomarc'h A, Lauvin L, Boudjema K, Messner M, et al. Indication of liver transplantation in severe alcoholic liver cirrhosis: quantitative evaluation and optimal timing. *J Hepatol* 2002;36:93-98.
  33. Lucey MR. Is liver transplantation an appropriate treatment for acute alcoholic hepatitis? [review]. *J Hepatol* 2002;36:829-831.
  34. Neuberger J, Schulz KH, Day C, Fleig W, Berlakovich GA, Berenguer M, et al. Transplantation for alcoholic liver disease. *J Hepatol* 2002;36:130-137.