INVITED REVIEW

THE TREATMENT OF ALCOHOLIC HEPATITIS

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Abstract — Alcoholic hepatitis is a precirrhotic lesion; it develops in only a minority of chronic alcohol abusers even after decades of abuse. The clinical spectrum of disease varies from asymptomatic hepatomegaly to florid hepatocellular failure with gastrointestinal bleeding and hepatic encephalopathy. Corresponding variation is observed both in morbidity and mortality. The majority of individuals with mild to moderate alcoholic hepatitis improve significantly following abstinence from alcohol and the provision of a diet sufficient to meet their nutritional requirements, their long-term outcome is determined largely by their ability to maintain abstinence from alcohol. Individuals with severe alcoholic hepatitis require intensive nutritional support and vigorous management of the complications of their liver injury; their outcome is generally poor. A small, carefully selected subgroup of these very sick patients may benefit, at least in the short-term, from treatment with corticosteroids; the place of orthotopic hepatic transplantation in this patient group, is still the subject of debate. No other treatment modalities have been shown to confer benefit consistently. A number of new therapeutic approaches have been proposed and need to be explored.

INTRODUCTION

Alcoholic hepatitis develops in only a minority of chronic alcohol abusers, even after decades of abuse (Lelbach, 1966; Leevy, 1968). An unknown percentage of individuals with this condition remain asymptomatic and do not come to medical attention; their liver injury may then heal in response to abstinence from alcohol, or else may evolve silently to alcoholic cirrhosis over time, particularly with continued drinking (Morgan, 1991). Individuals with alcoholic hepatitis may come to medical attention when incidentally found to have abnormal liver function tests or asymptomatic hepatomegaly. Alternatively, they may present with complications such as jaundice, ascites, gastrointestinal bleeding and hepatic encephalopathy (Morgan, 1991). Symptomatic individuals show variable morbidity and mortality both in the short- and long-term (Morgan, 1996). Progression to cirrhosis is observed more commonly in women, in individuals who present with severe disease and in those who continue to abuse alcohol.

For individuals with mild to moderate alcoholic hepatitis, the main therapeutic manoeuvres are the removal of alcohol and the provision of nutritional support. Further measures are required in individuals who present with severe alcoholic hepatitis in whom the short-term mortality rate may be as high as 60% (Morgan, 1996). A number of treatment options have been used in this patient population, but with varying degrees of success (Morgan, 1991; Mezey, 1993; Morgan, 1993; Ramond et al., 1993) (Table 1).

TREATMENT OPTIONS

Corticosteroids

Corticosteroids stimulate the appetite, increase hepatic albumin production and inhibit the production of Type I and Type IV collagen. In addition, they possess both anti-inflammatory and immunosuppressive properties. As such, they may benefit patients with alcoholic hepatitis.

Table 1. Potential treatments for alcoholic hepatitis

<table>
<thead>
<tr>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Hyperalimentation</td>
</tr>
<tr>
<td>Anabolic steroids</td>
</tr>
<tr>
<td>Insulin/glucagon</td>
</tr>
<tr>
<td>Colchicine</td>
</tr>
<tr>
<td>Propylthiouracil</td>
</tr>
<tr>
<td>D-Penicillamine</td>
</tr>
<tr>
<td>Hepatoprotective agents</td>
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<tr>
<td>Hepatic transplantation</td>
</tr>
</tbody>
</table>

© 1996 Medical Council on Alcoholism
Between 1971 and 1992 the results of 13, randomized, controlled trials of the effects of corticosteroids, in patients with alcoholic hepatitis, were published (Helman et al., 1971; Porter et al., 1971; Campra et al., 1973; Blitzer et al., 1977; Shumaker et al., 1978; Lesesne et al., 1978; Maddrey et al., 1978; Depew et al., 1980; Theodossi et al., 1982; Mendenhall et al., 1984; Bories et al., 1987; Carithers et al., 1989; Ramond et al., 1992). In addition, five separate meta-analyses of data from selected studies were undertaken and individually reported (Reynolds et al., 1989; Imperiale and McCullough, 1990; Daures et al., 1991; Poynard et al., 1991; Christensen and Gluud, 1995). Nevertheless, there is still no clear consensus as to the benefits of this form of treatment.

In the studies conducted to date, the severity of the liver lesion varied considerably both within and between study populations; this is reflected in the short-term mortality rates in the control patients, which ranged from 10 to 100% (Table 2). Histological confirmation of the diagnosis was obtained from 30 to 100% of individuals in the various series; between 50 and 93% of the individuals biopsied had established cirrhosis. Inclusion and exclusion criteria varied between studies; histological proof of diagnosis was an inclusion criterion in only three (Helman et al., 1971; Bories et al., 1987; Ramond et al., 1992); patients with gastrointestinal bleeding were excluded in most studies. Treatment regimens varied both in terms of the drugs used, the dosage and reducing schedules and the time periods employed (Table 2). However, the usual treatment regimen was prednisolone 40 mg daily for 4–6 weeks (Table 2). In all 13 studies the endpoint was death, usually in relation to the trial period or the hospital inpatient stay, although survival rates at 3 months or beyond were reported in some series.

In the first study, undertaken by Helman et al. (1971), 37 patients with alcoholic hepatitis, 27 (76%) of whom had underlying cirrhosis, were randomized to treatment with either prednisolone, 40 mg daily, reducing over 6 weeks, or to a placebo preparation. Details were not provided of the mortality rates at 1 month; however, the 3-month mortality rate was significantly lower in the steroid-treated patients (5%) than in the control group.

### Table 2. Controlled trials of corticosteroids in patients with alcoholic hepatitis of all grades of severity

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Daily drug dosage</th>
<th>Treatment period</th>
<th>Control group</th>
<th>Steroid group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patients n</td>
<td>Deaths* n (%)</td>
<td>Patients n</td>
</tr>
<tr>
<td>Helman</td>
<td>1971</td>
<td>40 mg prednisolone reducing oral</td>
<td>42</td>
<td>17</td>
<td>6 (35)</td>
</tr>
<tr>
<td>Porter</td>
<td>1971</td>
<td>40 mg methylprednisolone i.v. reducing oral</td>
<td>10</td>
<td>9</td>
<td>7 (78)</td>
</tr>
<tr>
<td>Campra</td>
<td>1973</td>
<td>0.5 mg/kg prednisolone reducing oral</td>
<td>14</td>
<td>25</td>
<td>9 (36)</td>
</tr>
<tr>
<td>Blitzer</td>
<td>1977</td>
<td>40 mg prednisolone reducing oral</td>
<td>26</td>
<td>15</td>
<td>7 (47)</td>
</tr>
<tr>
<td>Shumaker</td>
<td>1978</td>
<td>30 mg methylprednisolone i.v. reducing oral</td>
<td>21-24</td>
<td>7</td>
<td>2 (29)†</td>
</tr>
<tr>
<td>Lesesne</td>
<td>1978</td>
<td>40 mg prednisolone reducing oral</td>
<td>44</td>
<td>7</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Maddrey</td>
<td>1978</td>
<td>40 mg prednisolone reducing oral</td>
<td>28-32</td>
<td>31</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Depew</td>
<td>1980</td>
<td>40 mg prednisolone reducing oral</td>
<td>42</td>
<td>13</td>
<td>7 (54)</td>
</tr>
<tr>
<td>Theodossi</td>
<td>1982</td>
<td>1 g methylprednisolone i.v.</td>
<td>3</td>
<td>28</td>
<td>16 (57)</td>
</tr>
<tr>
<td>Mendenhall</td>
<td>1984</td>
<td>60 mg prednisolone reducing oral</td>
<td>30</td>
<td>88</td>
<td>18 (20)</td>
</tr>
<tr>
<td>Bories</td>
<td>1987</td>
<td>40 mg prednisolone oral/i.v. reducing oral</td>
<td>30</td>
<td>21</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Carithers</td>
<td>1989</td>
<td>32 mg methylprednisolone oral/i.v. reducing oral</td>
<td>42</td>
<td>31</td>
<td>11 (35)</td>
</tr>
<tr>
<td>Ramond</td>
<td>1992</td>
<td>40 mg prednisolone oral/i.v. reducing oral</td>
<td>28</td>
<td>29</td>
<td>16 (55)</td>
</tr>
</tbody>
</table>

*At end of trial period except Helman (3-month mortality rates) and Theodossi (30-day mortality rates).
†Trials in which treatment conferred significant benefit.
‡Values extrapolated from trial data and other publications.
§Combined results suggest significant treatment effect.
TREATMENT OF ALCOHOLIC HEPATITIS

Table 3. Effect of treatment with corticosteroids in patients with severe alcoholic hepatitis and spontaneous hepatic encephalopathy included in randomized, controlled, clinical trials

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Control group</th>
<th>Steroid group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Patients</td>
<td>Deaths*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>n (%)</td>
</tr>
<tr>
<td>Helman</td>
<td>1971</td>
<td>6</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Porter</td>
<td>1971</td>
<td>8</td>
<td>7 (88)</td>
</tr>
<tr>
<td>Campra</td>
<td>1973</td>
<td>10</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Blitzer</td>
<td>1977</td>
<td>2</td>
<td>1 (50)</td>
</tr>
<tr>
<td>Shumaker</td>
<td>1978</td>
<td>6</td>
<td>4 (67)</td>
</tr>
<tr>
<td>Lesesne</td>
<td>1978</td>
<td>7</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Maddrey</td>
<td>1978</td>
<td>10</td>
<td>6 (60)</td>
</tr>
<tr>
<td>Depew</td>
<td>1980</td>
<td>13</td>
<td>7 (54)</td>
</tr>
<tr>
<td>Theodossi</td>
<td>1982</td>
<td>14</td>
<td>10 (71)</td>
</tr>
<tr>
<td>Mendenhall</td>
<td>1984</td>
<td>58</td>
<td>13 (22)</td>
</tr>
<tr>
<td>Carithers</td>
<td>1989</td>
<td>19</td>
<td>9 (47)</td>
</tr>
<tr>
<td>Ramond</td>
<td>1992</td>
<td>10</td>
<td>6 (60)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>163</td>
<td>84 (52)</td>
</tr>
</tbody>
</table>

*At end of the trial period except Helman (3-month mortality rates) and Theodossi (30-day mortality rates).
†Trials in which treatment conferred significant benefit.
‡Values extrapolated from trial data and other publications.
§Combined results suggest significant treatment effect.

Between 1971 and 1987 a further nine studies of the effects of corticosteroids in patients with alcoholic hepatitis were published, none of which showed benefit (Tables 2 and 3) (Porter et al., 1971; Campra et al., 1973; Blitzer et al., 1977; Shumaker et al., 1978; Maddrey et al., 1978; Depew et al., 1980; Theodossi et al., 1982; Mendenhall et al., 1984; Bories et al., 1987). Four of these studies deserve separate mention.

Campra et al. (1973) randomized 45 patients with alcoholic hepatitis to treatment with either prednisolone, 0.5 mg/kg daily, reducing over 6 weeks, or to a placebo preparation. At the end of the treatment period, the mortality rates in the control group (36%) and in the steroid-treated group (35%) were comparable (Table 2). However, patients with severe alcoholic hepatitis complicated by the development of spontaneous hepatic encephalopathy appeared to benefit selectively from treatment; thus, in this subpopulation the mortality rates were 80% in the control and 50% in the steroid-treated patients (Table 3). This observation prompted workers from the same department to undertake a second study including only patients with severe alcoholic hepatitis complicated by the presence of hepatic encephalopathy (Depew et al., 1980). However, treatment did not confer significant benefit; the within-trial mortality rate was approximately subjects (35%) ($P < 0.01$). Maximum benefit was observed in the most severely ill patients; thus the mortality rate in patients with spontaneous hepatic encephalopathy, given steroids, was 11% compared with a mortality rate of 100% in their counterparts given the placebo preparation (Table 3).
50%, in both control and steroid-treated patients, with deaths occurring at similar rates and for similar reasons in both groups.

Maddrey et al. (1978) randomized 55 patients with alcoholic hepatitis of varying severity to treatment with either prednisolone, 40 mg daily, or a placebo preparation, for approximately 1 month. The 30-day mortality rates in the control (13%) and steroid-treated patients (4%) were comparable (Table 2), as were the hospital inpatient mortality rates of 19% and 13%. Nevertheless, all deaths occurred in the most severely ill patients and discriminant function analysis showed that treatment had a significant effect on survival. Further, these authors found that the formula:

$$\text{Discriminant function} = 4.6 \left( \frac{\text{prothrombin time}}{\text{control time}} \right) + \frac{\text{serum bilirubin (mg/dl)}}{17.1}$$

was useful in predicting survival; all deaths occurred in patients in whom the discriminant function exceeded 93 on entry into the study.

The largest study, to date, was undertaken by Mendenhall et al. (1984), who randomized 178 patients with alcoholic hepatitis to treatment with either prednisolone, 60 mg daily, reducing over 30 days, or a placebo preparation. The 30-day mortality rates were comparable in both control (20%) and steroid-treated (21%) groups (Table 2). Approximately two-thirds of the trial population had hepatic encephalopathy at the time of enrollment and of these ~20% died; again, however, steroids had no effect on the outcome in this subpopulation (Table 3).

In the last 6 years, two more carefully designed and executed studies have been published (Carithers et al., 1989; Ramond et al., 1992), both of which reported a significant effect of treatment with corticosteroids on outcome. Carithers et al. (1989) randomized 66 patients with alcoholic hepatitis, recruited from four centres, to treatment with either 32 mg of methylprednisolone, given orally or intravenously for 4 weeks, tapering over a further 2 weeks, or a placebo preparation. All patients had severe disease evidenced by the presence of either spontaneous hepatic encephalopathy or a discriminant function of >32, calculated from the modified formula:

$$\text{Discriminant function} = 4.6 \left( \frac{\text{prothrombin time}}{\text{control time}} \right) + \frac{\text{serum bilirubin (mg/dl)}}{17.1}$$

The 28-day mortality rate in the steroid-treated patients (6%) was significantly lower than in the patients receiving the placebo preparation (35%) \((P < 0.006)\) (Table 2). In the subgroup of patients with spontaneous hepatic encephalopathy, the mortality rate in the steroid-treated patients (7%) was again significantly lower than in the control group (47%) \((P < 0.02)\) (Table 3). This was a well-conducted study, but it has been criticized because the diagnosis of alcoholic hepatitis was not confirmed histologically, nor were data provided on outcome beyond the study period.

The most recent study, undertaken in two centres by Ramond et al. (1992), employed the same inclusion criteria and utilized a similar treatment regimen to that used by Carithers et al. (1989). In addition, however, the diagnosis of alcoholic hepatitis was confirmed histologically in all patients and the follow-up period was prolonged beyond 6 months. Sixty-one patients were randomized to treatment with either prednisolone 40 mg daily, or a placebo preparation, for 28 days. During the study, there were significantly fewer deaths among the steroid-treated patients (13%) than among the patients receiving the placebo preparation (55%) \((P < 0.001)\) (Table 2). Equally, the mean cumulative survival rates at 2 months and 6 months were significantly higher in the steroid-treated patients (88% and 84%) than in the patients who had received the placebo preparation (45% and 45%) (Fig. 1). Subgroup analysis showed that the use of steroids conferred significant benefit, independently of the presence of hepatic encephalopathy (Fig. 2).

Between 1989 and 1995, five separate meta-analyses of available studies were undertaken to determine whether treatment with corticosteroids affects short-term mortality in patients with alcoholic hepatitis (Reynolds et al., 1989; Imperiale and McCullough, 1990; Daures et al., 1991; Poynard et al., 1991; Christensen and Gluud, 1995). The results of these meta-analyses are conflicting. Thus, Imperiale and McCullough (1990) concluded that, provided patients with gastrointestinal bleeding were excluded, steroids reduced the short-term mortality in patients with acute alcoholic hepatitis and hepatic encephalopathy. Poynard et al. (1991) concluded that steroids significantly reduced mortality in patients with severe alcoholic hepatitis independently of the presence of hepatic encephalopathy, whereas
Christensen and Gluud (1995) concluded that steroids have no significant effect on mortality in patients with alcoholic hepatitis whether or not they have hepatic encephalopathy.

The results of these meta-analyses must be viewed with caution, bearing in mind the results of the two best conducted studies to date (Carithers et al., 1989; Raymond et al., 1992). Thus, overall, it would appear that corticosteroids do not affect outcome in patients with mild to moderate alcoholic hepatitis, although they may significantly improve outcome in a small subgroup of patients with severe disease. These individuals have a discriminant function in excess of 32 and are free of gastrointestinal bleeding, bacterial infection and significant renal failure.
Such individuals are, however, encountered infrequently; in the study by Carithers et al. (1989), only 66 patients fulfilling these criteria were recruited from four centres in 5 years, while in the study by Ramond et al. (1992), only 61 such patients were recruited from two centres in 3 years. Once identified, these individuals should be given 40 mg of prednisolone daily for 4 weeks, followed by 20 mg daily for 1 week and then 10 mg daily for a final week. The complications of treatment are surprisingly few, but patients should be carefully monitored.

The treatment regimen may need to be modified in patients with evidence of past or present infection with hepatitis B or C. Corticosteroids may reactivate or increase viral replication and this may have clinical consequences (Wands et al., 1975; Lok et al., 1991; Magrin et al., 1994); equally, withdrawal of corticosteroid treatment may be associated with the development of an acute hepatitis or even hepatic failure (Rakela et al., 1983; Thung et al., 1985). If these patients are to be treated at all, then the prednisolone dosage should probably be reduced and its withdrawal prolonged beyond 2 weeks.

**Nutritional supplementation**

Very little information is available on the nutritional requirements of patients with alcoholic hepatitis (Morgan, 1991; Müller et al., 1994; Nompleggi and Bonkovsky, 1994). In a study by Weber and Reiser (1982), it was shown that these patients need protein intakes in the region of 70-100 g daily to ensure positive nitrogen balance. It is also likely that their daily energy requirements are increased, but this has not been documented, to date. Dietary intake may be limited by anorexia and nausea with the result that a high percentage of total daily energy may be consumed as alcohol (Morgan, 1981). These patients are, in consequence, frequently malnourished and this has a detrimental effect on survival (Mendenhall et al., 1993). There is, therefore, a clear rationale for the provision of nutritional supplementation in this population.

A number of controlled studies have been undertaken, which show that, in general, nutritional supplementation may improve nutritional status and liver function in patients with alcoholic hepatitis, but that it does not, in itself, improve survival (Nasrallah and Galambos, 1980; Calvey et al., 1985; Diehl et al., 1985; Mendenhall et al., 1985; Naveau et al., 1986; Achord, 1987; Soberon et al., 1987; Simon and Galambos, 1988; Bonkovsky et al., 1991a,b; Mezey et al., 1991; Kearns et al., 1992).

A small number of studies have been undertaken in which nutritional supplements have been provided for patients with alcoholic hepatitis via oral or enteral routes (Calvey et al., 1985; Mendenhall et al., 1985; Soberon et al., 1987; Kearns et al., 1992). Mendenhall et al. (1985), for example, assessed the effects of oral nutritional support on outcome in 57 patients with moderate to severe alcoholic hepatitis. Thirty-four patients were given a standard hospital diet and were allowed to eat ad libitum. The remaining 23 patients were given the same diet together with a dietary supplement high in calories, protein and branched-chain amino acids; both groups were monitored over 30 days. At the end of the trial period improvements were observed in six of the nine variables used to assess nutritional status in the patients receiving the oral supplement, whereas these variables were either unchanged or else had deteriorated in the patients given the hospital diet alone; mortality rates were similar in the control (21%) and supplemented (17%) groups. These two dietary regimens were obviously not comparable as they were neither isocaloric nor isonitrogenous. Thus, it is not possible to draw any conclusions from this study on the benefits of nutritional supplementation over provision of a diet adequate in calories and protein consumed ad libitum.

Calvey et al. (1985) undertook a more detailed study in 64 patients with severe alcoholic hepatitis, all of whom were provided with a basic daily diet containing 1800-2400 kcal, 40-80 g of protein and 22 mmol of sodium. Twenty-one patients received an additional 65 g of conventional protein and 2000 non-protein calories daily, while a further 21 patients received 45 g of conventional protein, 25 g of branched-chain amino acids and 2000 non-protein calories daily. These supplements were given orally, enteraly or, if necessary, intravenously, for –3 weeks.

No differences were observed in mortality rates between the control (32%) and supplemented (38%) groups. Overall, the mortality rate was significantly higher in the patients who failed to achieve positive nitrogen balance independently.
of the dietary regimen used (58 vs 3%) 
\((P < 0.001)\). This confirms the observation made 
by Fiaccadori et al. (1984) that survival is signifi-
cantly decreased in patients with chronic liver 
disease who are unable to maintain nitrogen equi-
librium.

Kearns et al. (1992) randomized 31 patients with 
 alcoholic hepatitis to receive, for 28 days, either 
a standard hospital diet or the same diet supple-
mented with a casein-based, enteral feed. During 
the trial period, patients in the supplemented 
group showed a more rapid clearing of their encephalopathy, a significant fall in their mean 
serum bilirubin concentration and a significant 
increase in their mean antipyrine clearance. The 
mortality rates in the supplemented (13%) and 
non-supplemented (27%) groups were, however, 
not significantly different. This study has been 
criticized because the energy intake in the non-
supplemented group met only 80% of predicted 
requirements, whereas the intake in the sup-
plemented group exceeded predicted require-
ments by 70%. Likewise the daily protein intakes 
in the non-supplemented and supplemented 
groups were widely disparate (50 vs 103 g). Thus, 
conclusions are difficult to draw. However, these 
workers were able to show that it is possible to 
feed these patients enterally and that enteral feeds 
are well-tolerated. Similar conclusions were 
drawn by other workers (Soberon et al., 1987).

A total of seven controlled studies of the effects 
of parenteral nutritional supplements in patients 
with alcoholic hepatitis have been undertaken to 
date (Table 4) (Nasrallah and Galambos, 1980; 
Diehl et al., 1985; Naveau et al., 1986; Achord, 
1987; Simon and Galambos, 1988; Bonkovsky et 
al., 1991a,b; Mezey et al., 1991). Overall, the 
number of treated patients is small. The majority 
of patients appear to have had mild to moderate 
alcoholic hepatitis as evidenced by the mortality 
rates in the control populations which ranged from 
zero to 22%. Histological confirmation of the 
diagnosis was obtained from zero to 100% of 
patients in the various studies; between zero and 
100% of the individuals biopsied had established 
cirrhosis. Inclusion and exclusion criteria varied 
between studies. All subjects were given a well-
balanced, hospital diet which provided at least 
30 kcal/kg and 1 g of protein/kg daily and received 
oral supplements of multivitamins, folic acid and 
minerals. The experimental groups received, in 
addition, a parenteral infusion of standard amino

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Trial duration (days)</th>
<th>Control regimen (daily)</th>
<th>Experimental regimen (daily)</th>
<th>Control group</th>
<th>Treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasrallah</td>
<td>1980</td>
<td>25</td>
<td>Standard diet</td>
<td>Standard diet + i.v. 70 g a.a.*</td>
<td>18</td>
<td>17 0 (0)†</td>
</tr>
<tr>
<td>Diehl</td>
<td>1985</td>
<td>30</td>
<td>Standard diet + i.v. 130 g glucose</td>
<td>Standard diet + i.v. 52 g a.a. + 130 g glucose</td>
<td>10</td>
<td>5 0 (0)</td>
</tr>
<tr>
<td>Naveau</td>
<td>1986</td>
<td>28</td>
<td>Standard diet</td>
<td>Standard diet + i.v. 90 g a.a. + 2800 kcal as glucose &amp; lipid</td>
<td>20</td>
<td>20 1 (5)</td>
</tr>
<tr>
<td>Achord</td>
<td>1987</td>
<td>21</td>
<td>Standard diet</td>
<td>Standard diet + i.v. 43 g a.a. + 200 g glucose</td>
<td>14</td>
<td>14 1 (7)</td>
</tr>
<tr>
<td>Simon</td>
<td>1988</td>
<td>28</td>
<td>Standard diet + 132 g protein &amp; 3200 kcal orally</td>
<td>Standard diet + i.v. 70 g a.a. + 100 g glucose/50 g lipid</td>
<td>18</td>
<td>16 4 (25)</td>
</tr>
<tr>
<td>Bonkovsky</td>
<td>1991</td>
<td>21</td>
<td>Standard diet</td>
<td>Standard diet + i.v. 70 g a.a. + 100 g glucose</td>
<td>12</td>
<td>9 0 (0)</td>
</tr>
<tr>
<td>Mezey</td>
<td>1991</td>
<td>30</td>
<td>Standard diet + i.v. 130 g glucose</td>
<td>Standard diet + i.v. 52 g a.a. + 130 g glucose</td>
<td>26</td>
<td>28 6 (21)</td>
</tr>
</tbody>
</table>

\*a.a. = amino acids.
†Trial in which the experimental regimen conferred benefit.
acids with or without glucose and lipid. In two of the studies the control group received an intravenous infusion of glucose in addition to the standard diet, while in a third study individuals in the control group received an enteral supplement in addition to their standard diet. Treatment was continued for between 21 and 30 days. A wide range of variables were used to assess both liver function and nutritional status and these varied considerably between studies. In all seven studies, however, the end-point was death.

The results of these studies are extremely difficult to interpret because it is often unclear what comparisons workers were trying to make. In several, the comparison made was ostensibly of the effects on outcome of a nutritionally adequate diet against a regimen providing excess protein and calories. However, in the majority of these studies voluntary food intake was appreciably less than the amount offered and less than the amount required to sustain adequate nutritional status. In consequence, the comparisons made were effectively between regimens which were either nutritionally adequate or nutritionally inadequate.

Because of the difficulties inherent in interpretation of these data, conclusions cannot be drawn. However, a number of observations can be made; first, voluntary food intake is likely to be poor in patients with moderate to severe alcoholic hepatitis, with the result that they may not be able to attain optimal nutrient intake unaided; second, provision of adequate energy and protein intakes will result in improvement in nutritional status and liver function even in patients who are severely ill, but has little effect on short-term mortality; third, no appreciable adverse events are associated with the provision of high-calorie, high-protein nutritional supplements; these regimens are well-tolerated by even the most severely ill patients without exacerbation of fluid retention, azotaemia or hepatic encephalopathy.

Thus, it would seem essential to ensure that all patients with alcoholic hepatitis are adequately nourished. They should receive a minimum of 30 kcal/kg and 1 g of protein/kg daily and this should be given, whenever possible, by the oral or enteral route; if difficulties are encountered in meeting requirements, then a proportion should be given parenterally, preferably via a peripheral vein. Standard feeds and parenteral solutions should suffice. There is no evidence, at present, that provision of nutrients in excess of requirements confers any additional benefit.

**Anabolic steroids**

Anabolic steroids might benefit patients with alcohol-related liver disease because of their effects on nucleic acid and protein synthesis (Bengmark and Olsson, 1964). To date, three randomized, controlled studies have been undertaken on the effects of anabolic steroids in patients with alcoholic hepatitis (Mendenhall *et al.*, 1984; Bonkovsky *et al.*, 1991a,b; Mendenhall *et al.*, 1993).

In the first study, Mendenhall *et al.* (1984) randomized 173 men with moderate to severe alcoholic hepatitis to treatment with either oxandrolone, 80 mg daily, for 30 days, or a placebo preparation. The 30-day mortality rate was 13% in the moderately ill patients and 29% in the severely ill patients; treatment with oxandrolone did not affect the short-term outcome. In the individuals with moderately severe alcoholic hepatitis, who survived the first 30 days, a significant reduction was observed in the 6-month mortality rate in relation to treatment (3.5% vs 20%; \( P < 0.02 \)). No such beneficial effect was observed in patients with severe alcoholic hepatitis and overall survival rates at 30 months were similar in the oxandrolone and placebo-treated groups.

Bonkovsky *et al.* (1991a,b) randomized 39 patients with moderate to severe alcoholic hepatitis to 21 days' treatment with either oxandrolone 80 mg daily, oxandrolone plus intravenous amino acid supplementation, intravenous amino acid supplementation alone, or to so-called 'standard therapy'. No significant differences in outcome were observed between the four groups, although improvement in laboratory variables was most marked in individuals who received both oxandrolone and nutritional supplementation.

More recently, Mendenhall *et al.* (1993) randomized 273 men with moderate to severe alcoholic hepatitis to treatment with either oxandrolone, 80 mg daily, for 30 days, and then 40 mg daily for 60 days, or to a placebo preparation. The oxandrolone-treated patients received, in addition, a branched-chain amino acid-enriched, oral supplement which provided 60 g of protein and 1600 kcal daily, for 30 days, and then...
Table 5. Mortality rates in patients with alcoholic hepatitis in relation to their degree of malnutrition, their daily calorie intake and treatment with oxandrolone (modified from Mendenhall et al., 1993)

<table>
<thead>
<tr>
<th>Oxandrolone</th>
<th>Moderate malnutrition</th>
<th>Severe malnutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;2500 kcal/day</td>
<td>&lt;2500 kcal/day</td>
</tr>
<tr>
<td>Yes</td>
<td>4%</td>
<td>30%</td>
</tr>
<tr>
<td>No</td>
<td>28%</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>&gt;2500 kcal/day</td>
<td>&lt;2500 kcal/day</td>
</tr>
<tr>
<td></td>
<td>21%</td>
<td>59%</td>
</tr>
<tr>
<td></td>
<td>13%</td>
<td>45%</td>
</tr>
</tbody>
</table>

45 g of protein and 1200 kcal daily for the remaining 60 days.

Overall, the 6-month cumulative mortality rate was 35% in patients receiving oxandrolone and nutritional supplementation and 39% in the control subjects. No selective beneficial effect was observed in relation to disease severity as in the original study carried out by this group (Mendenhall et al., 1984). However, a selective beneficial effect of treatment was observed in relation to the degree of malnutrition. Thus, in patients with moderate malnutrition, the 6-month mortality rate was significantly lower in patients receiving the active treatment regimen than the control regimen. No such effect was observed in the patients with severe malnutrition.

In order to reconcile the results of their two trials and to try to separate the beneficial effects of nutritional supplementation from those of oxandrolone, the above group, combined their two study populations and re-analysed their data (Mendenhall et al., 1993). They showed that patients with alcoholic hepatitis who were moderately malnourished benefitted from treatment with oxandrolone, provided that their oral intake, whether supplemented or not, exceeded 2500 kcal/day (Table 5). In these individuals, the 6-month mortality rate was 4% compared to mortality rates of between 28% and 33% in their counterparts whose dietary intake was inadequate or who were not receiving the anabolic steroid (Table 5). In patients with alcoholic hepatitis and severe malnutrition, oxandrolone had no effect on outcome but mortality was significantly lower in those individuals consuming in excess of 2500 kcal/day (19% vs 51%; P < 0.001) (Table 5).

These workers finally concluded that patients with alcoholic hepatitis need vigorous nutritional support, and if they are moderately malnourished they should also be given oxandrolone, although they did not suggest a treatment regimen. Oxandrolone is a relatively inexpensive drug and its use in the studies to date has been associated with few side-effects. It probably deserves further study.

**Insulin and glucagon**

A number of factors are known to control hepatic regeneration in animals, of which the best studied are insulin and glucagon (Baker, 1985). It seems reasonable to assume that the mechanisms controlling hepatic regeneration in humans are similarly regulated; the use of hepatotrophic factors in the treatment of alcoholic hepatitis is based on this assumption. To date, six randomized, controlled trials of insulin and glucagon in the treatment of alcoholic hepatitis have been undertaken (Baker et al., 1981; Mirouze et al., 1981; Radvan et al., 1982; Feher et al., 1987; Bird et al., 1991; Trinchet et al., 1992) (Table 6).

The results of the first trial, that by Baker et al. (1981), were encouraging, if inconclusive. Thus, although mean serum bilirubin concentrations and prothrombin times improved to a significantly greater degree in the patients receiving insulin and glucagon, the 21-day mortality rates in the control (24%) and treated patients (12%) were not significantly different (Table 6).

Similarly encouraging but more conclusive results were reported by Feher et al. (1987). In their study, the mean serum bilirubin concentration, serum aspartate transaminase and γ-glutamyl transeptidase activities and prothrombin time improved significantly in the treatment group, whilst only the mean serum bilirubin concentration showed improvement in the control group, and then to a lesser degree. In addition, the 21-day mortality rate in the treated patients (15%) was significantly less than in the control subjects (42%) (P < 0.02) (Table 6).

No significant benefits of treatment were, however, reported in the remaining four studies (Mrouze et al., 1981; Radvan et al., 1982; Bird et
Table 6. Effect of treatment with insulin and glucagon in patients with alcoholic hepatitis included in randomized, controlled, clinical trials

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Trial duration (weeks)</th>
<th>Insulin (U/24 h)</th>
<th>Glucagon (mg/24 h)</th>
<th>Control group</th>
<th>Treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patients n</td>
<td>Deaths n (%)</td>
</tr>
<tr>
<td>Baker</td>
<td>1981</td>
<td>3</td>
<td>24</td>
<td>2.4</td>
<td>25</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Mirouze</td>
<td>1981</td>
<td>2</td>
<td>36</td>
<td>4.0</td>
<td>12</td>
<td>7 (58)</td>
</tr>
<tr>
<td>Radvan</td>
<td>1982</td>
<td>2</td>
<td>48</td>
<td>4.8</td>
<td>15</td>
<td>7 (47)</td>
</tr>
<tr>
<td>Feher</td>
<td>1987</td>
<td>3</td>
<td>30</td>
<td>3.0</td>
<td>33</td>
<td>14 (42)</td>
</tr>
<tr>
<td>Bird</td>
<td>1991</td>
<td>3</td>
<td>30</td>
<td>3.0</td>
<td>43</td>
<td>14 (33)</td>
</tr>
<tr>
<td>Trinchet</td>
<td>1992</td>
<td>3</td>
<td>30</td>
<td>3.0</td>
<td>35</td>
<td>5 (14)</td>
</tr>
</tbody>
</table>

163 53 (33) 168 43 (26)

*Trial in which treatment conferred significant benefit.

Hypoglycaemia was observed, as a complication, in all of these studies and resulted in the death of at least one treated patient (Baker et al., 1981). In addition, a number of difficulties arose in maintaining intravenous access for prolonged periods of time. Given the potential complications and complexity of this form of treatment, and the limited evidence of its efficacy, its use is not to be recommended. A better understanding of the mechanisms controlling hepatic regeneration, in man, might result in the development of more useful treatment regimens.

Colchicine

Colchicine inhibits granulocyte migration into areas of inflammation and interferes with the degradation of polymorphonuclear leucocytes (Malawista, 1975). It also inhibits microtubule assembly (Olmstead and Borisy, 1973) and the transcellular movement of collagen (Ehrlich and Bornstein, 1972), and increases collagenase activity (Harris and Krane, 1971). Thus, on theoretical grounds, it might attenuate the inflammatory response associated with alcohol-related hepatocyte injury, and might diminish collagen deposition and enhance its dissolution.

Two randomized, controlled studies of colchicine in the treatment of alcoholic hepatitis have been undertaken, neither of which reported benefit (Trinchet et al., 1989b; Akriviadis et al., 1990). Thus, Akriviadis et al. (1990) treated 72 patients with severe alcoholic hepatitis with either colchicine, 1 mg daily, or a placebo preparation, for 30 days, and recorded death rates of 17% in the control and 19% in the colchicine-treated group. Similarly, Trinchet et al. (1989b) treated 67 patients with histologically-proven alcoholic hepatitis, 50% of whom had cirrhosis, with either 1 mg of colchicine daily, or a placebo preparation, for 6 months; liver biopsies were repeated at 3 and 6 months. Overall, no significant differences were observed in clinical, laboratory or histological variables between the two groups, over the time-course of the study, although there was some evidence of preferential histological improvement in the colchicine-treated patients at 3 months. Almost 60% of patients were lost to follow-up during this trial, so that conclusions are difficult to draw.

Thus, there is no evidence, at present, that patients with alcoholic hepatitis benefit from treatment with colchicine, at least in the short-term.

Propylthiourosis

Both alcohol and hypoxia produce liver injury which is predominantly centrilobular in distribution. Oxygen consumption rates are increased in animals with alcohol-induced liver injury and, if the liver oxygen supply is reduced, centrilobular necrosis will develop (Israel et al., 1973, 1975a). These changes can be suppressed by thyroidectomy and abolished by use of propylthiouracil (Bernstein et al., 1975; Israel et al., 1975b). It has, therefore, been suggested that chronic alcohol abuse might produce a hypermetabolic state within the liver, in man, resulting in an increased demand for oxygen, and ultimately to centrilobular hypoxia. As such, treatment with propylthiouracil might attenuate or even abolish these changes.
To date, four randomized, controlled trials of propylthiouracil in the treatment of alcoholic hepatitis have been undertaken (Orrego et al., 1979; Hallé et al., 1981; Serrano-Cancino et al., 1981; Peirrugues et al., 1989).

In the first study, Orrego et al. (1979) randomized 133 patients with alcohol-related liver disease, 38 (29%) of whom had alcoholic hepatitis, to treatment with either 300 mg of propylthiouracil daily, or a placebo preparation, for 6 weeks. The patients with alcoholic hepatitis who received the active drug were said to show more rapid improvement in a number of clinical and laboratory variables than those who received the placebo preparation. However, few data were provided to support this assertion.

In the remaining three studies, treatment with propylthiouracil was reported to be of little benefit (Halle et al., 1981; Serrano-Cancino et al., 1981; Peirrugues et al., 1989). Hallé et al. (1981), for example, randomized 67 patients with severe alcoholic hepatitis to treatment with either 225 mg of propylthiouracil daily, or a placebo preparation, for 6 weeks, and were unable to show any beneficial effects of treatment on either morbidity or mortality. Approximately 20% of patients in both control and treatment groups died, while 13% of the treated patients became hypothyroid.

Thus, there is no evidence, at present, that patients with alcoholic hepatitis benefit from treatment with propylthiouracil. It should also be remembered that propylthiouracil itself can induce fatal hepatic necrosis (Limaye and Ruffolo, 1987).

**D-Penicillamine**

Penicillamine inhibits the cross-linkage of newly formed collagen thus rendering it more susceptible to the actions of collagenase (Nimni and Bavetta, 1965). It might, therefore, reduce or impede hepatic fibrogenesis and prevent progression of alcoholic hepatitis. Resnick et al. (1974) randomized 40 patients with moderately severe alcoholic hepatitis to treatment with either D-penicillamine, 1 g daily, or a placebo preparation, for 8 weeks. Similar improvements were observed in mean serum bilirubin concentrations and aspartate aminotransferase activities in both groups during the trial and the mortality rates of 19% in the control and 16% in the penicillamine-treated patients were comparable. There were reductions in the degree of hepatocellular necrosis and in the active deposition of collagen in liver biopsies obtained from both groups of patients, but the improvements appeared greater in the patients receiving the penicillamine. However, the number of paired pre- and post-treatment biopsies was too small for adequate statistical analysis of these histological changes in relation to treatment. Further short- and long-term studies of penicillamine in the treatment of alcoholic hepatitis are needed.

**Hepatoprotective agents**

A number of so-called ‘hepatoprotective agents’ are available and are used extensively, particularly in Continental Europe, for the treatment of alcoholic liver disease (Morgan, 1985). However, the evidence that their use confers any significant benefit is poor.

**(+)-Cyanidanol-3 (Catechin)** is the best known and most extensively investigated hepatoprotective agent (Morgan, 1985). It is a naturally occurring bioflavonoid which has antioxidant and membrane-stabilizing properties and an ability to scavenge free radicals. It has been shown to normalize the NADH/NAD⁺ ratio, to increase ATP concentrations, and to stabilize lysosomal membranes in the livers of rats with alcohol-related liver injury. Two short-term, double-blind, randomized, controlled trials of (+)-cyanidanol-3 in patients with alcoholic hepatitis have been undertaken, to date (Henning, 1981; Sanchez-Tapias et al., 1981); no significant effects of treatment were observed after 2 weeks or 3 months of therapy.

**Thioctic acid (α-lipoic acid)** is a naturally occurring compound which is a cofactor in the pyruvate dehydrogenase and α-ketoglutarate dehydrogenase enzyme complexes forming part of the citric acid cycle; it also stimulates prostaglandin synthesis via its action on prostaglandin cyclooxygenase (Morgan, 1985). Apart from some evidence to suggest that it may be of value in treating liver failure following *Amanita phalloides* poisoning, reports of its beneficial effects in liver disease are largely anecdotal. Marshall et al. (1982) undertook a double-blind, randomized, controlled trial of thioctic acid, over 6 months, in patients with pre-cirrhotic, alcohol-related liver disease, including several with histologically proven alcoholic hepatitis. No beneficial effects of treatment were observed additional to those...
Individuals depend on social support which could worsen their overall prognosis; second, they may consider transplant programmes because of the presence of their alcohol-related disorders. Patients are rigorously evaluated before being accepted by transplant services, and it is to be assumed that other organ damage is diligently sought, and, if identified and found to be clinically significant, would be a contraindication, relative or definite, to candidacy.

Where transplantation has been undertaken in patients with alcoholic liver disease, outcomes are good, both in terms of survival and quality of life, and do not differ substantially from those reported in patients with non-alcoholic liver disease (Bird et al., 1990; Kumar et al., 1990; Knechtle et al., 1992; Lucey et al., 1993) (Fig. 3). Importantly, it increases 2-year survival in the patients with the most severely decompensated disease (Poynard et al., 1994).

It was initially suggested that only individuals who had successfully abstained from alcohol for 6 months or more should be considered as transplant candidates in order to lessen the risk of recidivism post-transplantation. Starzl et al. (1988), however, refuted this suggestion and showed, in an early series, that 1-year recidivism rates were low even in individuals drinking up to the time of transplantation. Campbell et al. (1993) warned, however, that early recidivism rates should be treated with caution, because in their series the early recidivism rate of 11.5% rose to 32% by 3 years post-transplant. In many of the reported series recidivism rates were consistently higher in individuals who were drinking up to the time of transplantation compared with those who were abstinent beforehand (Bird et al., 1990; Kumar et al., 1990). Indeed, Osorio et al. (1994) have shown that the single most important predictor of abstinence post-transplantation is abstinence before the transplant procedure. However, this view has recently been challenged by Howard et al. (1994), following their controlled assessment of 20 individuals who had been transplanted for alcoholic liver disease some 1–6 years previously. All had remained abstinent from alcohol in the 7–10 months following surgery when medical supervision was at its closest, but there-
Fig. 3 Actuarial patient survival after liver transplantation for alcoholic (■; n = 41) and non-alcoholic (○; n = 93) liver disease in adult recipients (Knechtle et al., 1992)

after 80% had returned to drinking. Although the mean alcohol intake was relatively modest at 25 g daily, 40% were drinking above ‘low-risk’ levels, defined as 112 g/week for women and 168 g/week for men, 50% were binge-drinking intermittently, and 15% were drinking heavily and regularly. There was no relationship between alcohol consumption post-transplantation and the duration of abstinence before the procedure.

The return to drinking post-transplantation is obviously not without consequence. Campbell et al. (1993) showed that 18% of their transplant recipients were abusing alcohol sufficiently severely to require admission to hospital. Perhaps more disturbing is the observation that severe alcoholic liver injury develops rapidly in the grafted liver in individuals who return to drinking (Baddour et al., 1992). Thus, in a group of 23 liver graft recipients who continued to abuse alcohol post-transplantation, histological evidence of alcoholic hepatitis was observed in all 23 within 77–579 days of transplantation, whereas cirrhosis was observed in four (Baddour et al., 1992). Howard et al. (1994) reported on liver biopsies undertaken a mean of 36 months post-transplantation in eight patients, two of whom had returned to regular heavy drinking; cirrhosis was evident in the biopsies from both of these patients.

The majority of patients with alcoholic liver disease who are transplanted have end-stage cirrhosis. There are very few reports of transplantation being undertaken for alcoholic hepatitis per se. Bonet et al. (1993) have recently documented their experience of transplanting cirrhotic individuals with and without superadded alcoholic hepatitis. The 1-year survival rates in the patients with cirrhosis alone (81%) and in those with cirrhosis and alcoholic hepatitis (89%) were comparable. However, the 1-year post-transplant sobriety rate was 89% in the patients with cirrhosis alone, but only 51% in the patients with superadded alcoholic hepatitis. No details were given of the patients’ drinking behaviour pre-transplantation, but it is reasonable to assume that the patients with alcoholic hepatitis were more likely to have been actively abusing alcohol.

The results of this study have given rise to the suggestions that the use of transplantation as a treatment option for patients with alcoholic hepatitis has no place outside the setting of a well-designed controlled trial (Miller et al., 1994) or that it should be abandoned altogether (Sorrell et al., 1994). Therefore, at present, no conclusions can be drawn about the place of hepatic transplantation as a treatment for acute alcoholic hepatitis.

POTENTIAL NEW THERAPEUTIC APPROACHES

A number of potential new therapeutic ap-
approaches to the treatment of alcoholic hepatitis have been identified (Mezey, 1993), some of which are currently under investigation.

Lieber et al. (1994) have shown that oral supplementation with phosphatidylcholine prevents the development of alcohol-related fibrosis and cirrhosis in non-human primates. They have identified the active agent as dilinoleoylphosphatidylcholine and have shown that it most likely produces its beneficial effects by promoting collagen breakdown. Clinical trials in patients with alcoholic liver disease are currently underway. Collagen degradation could also be enhanced by insertion of exogenous DNA encoding amino or carboxyterminal peptides of procollagen into hepatocytes (Wu et al., 1986). Alternatively, steps could be taken to inhibit collagen synthesis, for example, by use of proline analogues.

Cytokines, such as tumour necrosis factor, may enhance hepatic necrosis and fibrosis and have been implicated in the genesis of alcoholic hepatitis (McClain et al., 1993). The development of antibodies to the relevant cytokines or to their receptors might provide a useful therapeutic approach. Similarly, free oxygen radicals have been implicated in the genesis of alcohol-related liver injury (Nordman et al., 1992), so that steps either to block their formation or to enhance their metabolism might prove therapeutically beneficial (Nordmann, 1994).

Finally, once the factors governing hepatic regeneration have been fully identified it might be possible to stimulate the process and so enhance recovery from alcohol-related liver injury.

**A RATIONAL APPROACH TO TREATMENT**

The majority of patients with mild to moderate alcoholic hepatitis will improve significantly following abstinence from alcohol and the provision of a diet sufficient to meet their nutritional needs. In general, therefore, they should ingest a minimum of 30 kcal and 1 g of protein per kg body weight daily. Dietary intake should be carefully monitored and additional oral supplements provided as indicated. If an adequate oral intake is not achieved within 48 h, then nasogastric or nasojejunal feeding should be instituted. If nutritional requirements still cannot be met, then parenteral feeding may be used, preferably using the peripheral route.

The outcome in patients with mild to moderate alcoholic hepatitis is determined, to a large extent, by their ability to maintain abstinence from alcohol. They should be carefully monitored over time.

Patients with severe alcoholic hepatitis are less easily managed as the majority will already have cirrhosis. Many present with severe hepatocellular failure with jaundice, ascites and hepatic encephalopathy and/or with the complications of portal hypertension such as hypersplenism and bleeding oesophageal varices. Deterioration in their clinical status and laboratory variables is commonly seen following admission; the development of renal failure usually heralds a fatal outcome.

These patients should be managed in a specialist liver unit with the facilities to treat the complications of their liver disease; they should receive intensive nutritional support. A small subgroup of carefully selected patients may benefit, at least in the short-term, from treatment with corticosteroids. No firm recommendation can be made about the value of other treatment modalities at present. The place of hepatic transplantation for these extremely sick patients is still the subject of debate.

The mortality rate in this population is high, exceeding 60% in some series. The outcome in the survivors is, as in the patients with less severe disease, determined largely by their ability to remain abstinent from alcohol. They need careful long-term monitoring.

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