Q J Med 2003; **96**:391–400
doi:10.1093/qjmed/hcg076

Review

QJM

Recent developments in the treatment of alcoholic hepatitis

R. MADHOTRA and I.T. GILMORE[1]

From the Milton Keynes General Hospital, Milton Keynes, and [1]Royal Liverpool University Hospital, Liverpool, UK

Summary

Alcoholic hepatitis is a form of acute injury to liver tissue that is also a precursor of cirrhosis, and carries significant morbidity and mortality. Severe alcoholic hepatitis in particular carries a high short-term mortality, and also places an enormous burden on stretched healthcare resources. Treatment of alcoholic hepatitis has been limited to supportive management and nutritional supplementation without clear improvements in outcome, and the timing and patient selection for hepatic transplantation is problematic. The use of corticosteroids has remained controversial for many years, but probably has a role in selected patients. Various other therapeutic strategies have been tested over the decades and none has shown any consistent benefit. Recently there have been major developments in our understanding of the mechanisms of alcoholic liver injury, including the role of cytokines and hepatocyte apoptosis. For the first time, there are exciting possibilities for specific therapies for this challenging and serious condition.

Introduction

Alcoholic hepatitis is a serious disease, with a mortality of up to 60% in the first 4 weeks of diagnosis in severe cases.[1] Those that survive may spend weeks or months in hospital on supportive treatment only, and are a significant burden on our already stretched hospital services.[2,3] The syndrome of alcoholic hepatitis develops in only a minority of chronic alcohol abusers,[4] with a clinical spectrum ranging from an asymptomatic histological diagnosis to a life-threatening clinical illness that may include jaundice, ascites, gastrointestinal bleeding or encephalopathy. Lack of understanding of mechanisms of liver cell injury in alcoholic hepatitis has hampered the development of effective treatments, but recent advances in our understanding of the pathogenesis of this disease have led to new treatment options. We discuss various treatment options for alcoholic hepatitis, with emphasis on these recent developments. In particular, the potential role of inflammatory cytokines and of oxidative stress has become clearer, although their interactions with immune mechanisms, and the role of apoptosis, remain uncertain.

Corticosteroids

The main rationale for use of corticosteroids in alcoholic hepatitis is to suppress the activated immune response that is elicited by enhanced generation of neo-antigens, including liver-specific lipoproteins, Mallory bodies and liver membrane antigens. Corticosteroids also have anti-inflammatory properties and inhibit the synthesis of

Address correspondence to Professor I.T. Gilmore, Department of Gastroenterology, Link 5-Z, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP. e-mail: igilmore@liv.ac.uk

cytokines.[5] The most intensively studied treatment of alcoholic hepatitis, corticosteroids are the yardstick against which newer treatments must be measured. There have been 12 randomized controlled trials, five showing a reduction in mortality,[6–10] and seven no benefit.[11–17] The inclusion and exclusion criteria varied between the studies, with only two[6,9] requiring histological confirmation of diagnosis as an inclusion criterion. Disease severity also varied considerably between studies, as is evident from the short-term mortality rates, which ranged from 10% to 100%. The treatment regimens, duration and dosage also differed between studies. Because of the complications of steroid treatment, most studies excluded patients with gastrointestinal bleeding, active infection, renal failure and pancreatitis. Two well-designed studies[9,10] need special mention, both using similar inclusion criteria and treatment regimens. Patients with severe alcoholic hepatitis (Maddrey's discriminant function >32) were included in these studies, and both showed significant improvement in 30-day hospital survival with steroid treatment.

Three meta-analyses of these randomized controlled trials[18–20] have been performed to determine whether treatment with corticosteroids affects short-term mortality in patients with alcoholic hepatitis. Two of these[18,19] concluded that corticosteroids reduced the short-term mortality in patients with acute alcoholic hepatitis. While the first meta-analysis[18] concluded that corticosteroids provided this short-term mortality benefit only in patients with both alcoholic hepatitis and hepatic encephalopathy, the second[19] showed that the protective effect of steroids was independent of hepatic encephalopathy in their patient group. However the third meta-analysis by Christensen and colleagues[20] did not find any improvement in short-term mortality from steroid therapy, although the authors did point out the inadequacies of the published studies in failing to characterize a subset of patients with severe alcoholic hepatitis who might benefit from corticosteroids.

Recently, another meta-analysis[21] was conducted on data from American and French randomized controlled trials to study the efficacy of corticosteroids in severe alcoholic hepatitis. The analysis was conducted on patients with Maddrey's discriminant function >32, using the pooled data from three randomized controlled trials. There were 215 patients (102 placebo, 113 corticosteroid group). At 28 days, the survival was significantly higher in the corticosteroid than in the placebo group (84.6±3.4% vs. 65.1±4.8%, $p = 0.001$). Once again, age ($p = 0.0001$), serum creatinine ($p = 0.002$) and corticosteroid treatment ($p = 0.002$) were the independent prognostic factors. There was also significant decrease in bilirubin levels at 7 and 14 days in patients treated with corticosteroids. This study concluded that corticosteroids improved the short-term survival of patients with severe alcoholic hepatitis.

Overall, the available evidence supports use of corticosteroids in carefully selected patients with severe alcoholic hepatitis (as defined by Maddrey's discriminant function >32, and/or hepatic encephalopathy). It is imperative that the diagnosis of alcoholic hepatitis is made with certainty, which necessitates liver biopsy, often by the transjugular route. Also, active infections, gastrointestinal bleeding and renal failure must be excluded in these patients before treatment because of the adverse effect of steroids on these conditions.

TNF-α inhibitors

In 1989, McClain and colleagues[22] described alterations in tumour necrosis factors (TNF) metabolism in alcoholic hepatitis. They demonstrated that cultured peripheral blood monocytes from patients with alcoholic hepatitis spontaneously produced TNF, and had an enhanced TNF response to an endotoxin lipopolysaccharide stimulus. Subsequently other investigators demonstrated that a cytokine-induced acute inflammatory response is one underlying basic mechanism responsible for cellular injury in alcoholic hepatitis.[23–25] Serum TNF was elevated in patients with acute alcoholic hepatitis, particularly in the more severe cases, and TNF levels correlated with mortality.[22,26] TNF was also detected in ballooned hepatocytes containing alcoholic hyaline bodies.[27] Grove and colleagues[28] linked a TNF promoter polymorphism (-238) with susceptibility to alcoholic steatohepatitis, and suggested that alcohol drinkers who develop alcoholic hepatitis may be genetically predisposed. Subsequently a functional polymorphism (-308) has been linked to increased susceptibility to alcoholic liver disease.[29] TNF-inducible cytokines like IL-6 and IL-8 are also elevated in alcoholic hepatitis, and levels correlate with markers of the acute-phase response, liver function and clinical outcomes.[30,31]

TNF-α antibodies (infliximab) have shown promising results in some chronic inflammatory diseases like Crohn's disease and rheumatoid arthritis. There has been some concern about their use, in case liver regeneration might be adversely affected by TNF-α suppression. However, in a pilot study in 12 patients, the drug was well tolerated in a single infusion, caused suppression of inflammatory

cytokines, and was associated with an improvement in Maddrey's discriminant function.[32] However, these observations were uncontrolled. Recently, Spahr *et al*.[33] studied the safety and effectiveness of infliximab in combination with steroids in patients with severe alcoholic hepatitis. Twenty patients with biopsy-proven alcoholic hepatitis and Maddrey's discriminant function >32 received prednisone 40 mg/day for 28 days and either intravenous infliximab (5 mg/kg) or placebo at day 0. The study showed reduction in TNF-inducible cytokines such as IL-6 and IL-8 at day 10. Although there was no histological improvement, there was significant improvement of Maddrey's score at day 28. These encouraging results will lead the way for larger trials studying infliximab in severe alcoholic hepatitis.

Pentoxifylline (PTX) is a non-selective phosphodiesterase inhibitor. PTX inhibits synthesis of TNF by increasing the intracellular concentrations of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). PTX has been shown to decrease TNF gene transcription.[34] Subsequent studies[35–37] reported that PTX inhibits synthesis of cytokines (including monocyte chemoattractant protein-1, IL-6, IL-8, macrophage inflammatory protein 1a and 1b), decreases activation of neutrophils, and reduces proliferation of monocytes and lymphocytes. On the basis of its property to down-regulate cytokine production, PTX was used as a potential therapeutic agent for alcoholic hepatitis, showing that the increase in TNF levels could be prevented by the use of PTX.[38] In this pilot study, the authors also showed that there was reduction in hepatorenal failure with a trend towards improved survival of patients treated with PTX.

Recently Akriviadis and colleagues[39] published the results of a prospective, randomized double-blind study of PTX in 102 patients (1 drop-out) with severe alcoholic hepatitis (Maddrey's discriminant function $\geq$32). Forty-nine patients received PTX 400 mg orally three times daily, and 52 patients received placebo vitamin B12 for 28 days. The endpoints of the study were: (a) short-term survival during index admission; and (b) development of hepatorenal syndrome. This study showed that pentoxifylline improves 28-day mortality in patients with severe alcoholic hepatitis. Twelve (24.5%) PTX-treated patients died, compared with 24 (46.1%) control patients ($p = 0.037$; RR 0.59; 95%CI 0.35–0.97). The survival benefit in PTX-treated patients appeared to be due to a significant decrease in the risk of developing hepatorenal syndrome. Six of 12 (50%) PTX-treated patients died of renal failure, compared with 22/24 (92%) placebo group patients ($p = 0.009$; RR 0.29; 95%CI 0.13–0.65). On multivariate analysis, age, serum creatinine at randomization and PTX treatment were independent predictors of survival. Baseline values of TNF were not predictive of survival. TNF levels correlated with serum creatinine at randomization and during the hospital course, suggesting that raised levels of cytokine were implicated in pathogenesis of renal failure, but there was no significant decrease in TNF levels in patients treated with PTX. Overall, this study showed marked reduction in development of hepatorenal syndrome and a significant reduction in mortality in patients with severe alcoholic hepatitis who were treated with 400 mg PTX three times daily for 28 days. However, the mechanisms underlying these benefits are not clearly explained in this particular study. Although PTX appears to represent a significant advance, multicentre controlled studies are needed to confirm its effectiveness and elucidate its mode of action before it can be recommended as the standard treatment for alcoholic hepatitis.

N-Acetylcysteine and other antioxidants

Oxidative stress is a well-established feature of alcohol-induced liver cell injury, attributable to both an increased production of reactive oxygen species and a depletion of antioxidant defences.[40–42] Oxidative stress leads to apoptosis by inducing Fas ligand expression.[43] Antioxidants would therefore appear to have anti-apoptotic activities. Repletion of glutathione stores by N-acetylcysteine may also help through clearing the pro-apoptotic reactive oxygen species.

N-Acetylcysteine has anti-oxidant, anti-cytokine and anti-apoptotic properties, and therefore may be useful in counteracting some of the underlying mechanisms in the pathogenesis of alcoholic hepatitis. It can be safely administered to patients with fulminant liver failure of various causes, and has been reported to reduce mortality in these patients.[44,45] Moine *et al*.[46] presented the results of a pilot study of 16 patients with biopsy-proven active alcoholic hepatitis who were treated with N-acetylcysteine. All patients had a Maddrey's discriminant function of >32, and had had no improvement in liver function tests in the previous 1 week. N-Acetylcysteine was administered in a dose of 300 mg/kg/day for 7 days (five patients) or 14 days (11 patients). The 30-day survival rate was 56% in patients treated with N-acetylcysteine. All the patients had a significant decrease in aspartate transaminase, alkaline phosphatase and prothrombin time. Total bilirubin levels decreased

from 160 μmol/l before the treatment to 130 μmol/l (at day 5; $p<0.05$) and to 110 μmol/l (at day 7; $p<0.05$) in patients with a Maddrey's discriminant function of <50. The authors concluded that N-acetylcysteine could be safely administered in cirrhotic patients with alcoholic hepatitis, with an improvement in some biological parameters. This uncontrolled study did not examine survival benefit.

Vitamins A and E, and carotenoids are important plant-derived antioxidants. The plasma concentrations of these antioxidants are extremely low in patients with acute alcoholic hepatitis when compared to historical controls ($p<0.05$).[47] Cox *et al.*[48] studied a combination of antioxidants (vitamins C and E) and ursodeoxycholic acid, a membrane-stabilizing agent, and found it as effective as corticosteroids. The results of this small, non-randomized retrospective study (11 patients in combination group and 10 patients in steroid group) were encouraging enough to warrant a controlled trial.

Recently Phillips *et al.*[49] conducted a controlled trial comparing the effects of prednisone (30 mg o.d.) with an antioxidant cocktail (vitamins A,C,E, selenium, allopurinol, desferrioxime and N-acetylcysteine) with intralipid as membrane stabilizer. They studied 30-day mortality in a prednisolone-treated group (53 patients) and an antioxidant group (48 patients). Antioxidants had an adverse effect on 30-day mortality, leading to early termination of the trial. In another double-blind controlled study, the effect of N-acetylcysteine (150 mg/kg) combined with vitamins A–E, biotin, selenium, zinc, manganese, copper, magnesium, folic acid and coenzyme Q daily for 6 months in severe alcoholic hepatitis patients stratified by sex and steroid use was examined, and did not show any beneficial effect of antioxidant therapy on 180-day mortality.[50] Overall, the present data do not support antioxidants as a therapy in severe alcoholic hepatitis.

Nutrition

For decades it has been suspected that nutritional deficiencies play an important role in triggering the liver injury in alcohol abusers. It seemed common sense that nutritional supplements would benefit patients with long-standing alcohol misuse and alcohol-related liver disease. In 1986, a Veterans Affair Cooperative study showed that protein-calorie malnutrition was present in almost all patients with alcoholic hepatitis, and mortality rate in these patients correlated with severity of protein-calorie malnutriton.[51] The mortality rate in this study varied from 2% in patients with mild malnutrition to 52% in those with severe malnutrition. Better nutritional status also correlated with greater food intake and survival. Twelve prospective clinical trials have been undertaken to study nutritional supplementation as a primary treatment for alcoholic liver disease. Most have shown improvement in liver function and nutritional status, but very few showed any survival benefit. Five of the studies[51–55] used enteral nutritional supplements, and four other studies[51–53,55] did not find any differences in mortality rates. Only one study[54] showed improved survival with enteral nutrition. The remaining seven trials[56–61] looked at the use of parenteral aminoacid supplementation as primary treatment. Although most of these studies[57–61] showed improvement in liver function and/or histology, only one[57] showed a reduced mortality with intravenous amino acid supplements.

A recent multicentre prospective randomized study[55] compared total enteral nutrition and prednisolone in the treatment of severe alcoholic hepatitis. Seventy-one patients were randomized to receive either prednisolone 40 mg/day ($n=36$) with normal diet or nasoduodenal tube feeding (2000 kcal/day, $n=35$) for 28 days. There was no significant difference in 28-day mortality between the patients receiving steroids and those receiving total enteral nutrition (25% vs. 31%, respectively), but the mortality rate during follow-up was higher with steroid treatment (37% vs. 8%; $p=0.04$). Early deaths were more frequent with total enteral nutrition, whereas deaths were more frequent with steroids in the weeks after treatment, mainly because of infections. This study concluded that total enteral nutrition is as effective as steroid treatment in the short-term treatment of severe alcoholic hepatitis. It remains to be determined whether a combination of steroids and total enteral nutrition might be more effective than either alone.

Anabolic steroids

Anabolic steroids have been used to treat alcoholic hepatitis because of their ability to stimulate protein synthesis, cell repair and hepatic regeneration. These agents also improve nitrogen conservation, and may reverse the catabolic state in these generally ill patients. In what was initially a multicentre Veteran Affairs Cooperative trial,[11] Mendenhall *et al.* compared the effect of prednisolone, oxandrolone and placebo in patients with alcoholic hepatitis. There was no difference in the short-term outcome, but there was significant improvement in mortality rates with oxandrolone

treatment at 6 months ($p < 0.02$). They also found a survival benefit in moderate but not severe malnutrition when oxandrolone was added.[62] Recently, a systematic Cochrane review studying randomized clinical trials did not demonstrate any significant beneficial effects of anabolic-androgenic steroids on any clinically important outcomes of patients with alcoholic liver disease.[63] At present, use of anabolic steroids in alcoholic hepatitis cannot be recommended.

Propylthiouracil

Alcohol ingestion causes a hypermetabolic state that increases oxygen consumption, and may cause relative ischaemia in the perivenular (Rappaport Zone 3) region.[64] Propylthiouracil or surgically-induced thyroidectomy partially protects against hypoxia-induced liver injury in ethanol-fed animals.[65,66] Of the four randomized controlled trials[67–70] of propylthiouracil in the treatment of alcoholic hepatitis, only one study showed benefit in improvement of biochemistry. Also, propylthiouracil is itself a hepatotoxic drug, and various cases of fatal hepatic necrosis have been reported. A recent systematic review of randomized clinical trials using propylthiouracil in patients with alcoholic liver disease could not demonstrate any significant effect of propylthiouracil on important outcomes like mortality, liver-related mortality, liver complications and liver histology in patients with alcoholic liver disease.[71]

Colchicine

Colchicine inhibits the migration and degradation of polymorphonuclear leukocytes.[72] It also interferes with the transcellular migration of collagen and enhances the activity of hepatic collegenases.[73] Because of these properties, use of colchicine was studied in two randomized controlled studies[74,75] but neither showed any improvement in mortality.

Penicillamine

Penicillamine facilitates the activity of collagenase on the newly formed collagen by inhibiting the cross-linkage during its synthesis.[76] Only one randomized controlled trial has been conducted to study the use of penicillamine in alcoholic hepatitis, and no mortality benefit was found.[77]

Insulin and glucagon therapy

Hepatocyte proliferation is an important indicator of outcome in alcoholic hepatitis.[78] Insulin and glucagon are thought to play a role in hepatic regeneration in animal model.[79] Two randomized controlled trials[80,81] investigating use of insulin and glucagon in treatment of alcoholic hepatitis showed significant improvement in 21-day mortality rates, but three other trials[82-84] did not show any survival benefit. Hypoglycaemia was observed in almost all of these studies, including two hypoglycaemia-related deaths. Better understanding of the mechanisms of hepatic regeneration is still required.

Calcium-channel blockers

Calcium-channel blockers have been shown to have a hepatoprotective effect in animal models of alcohol-induced liver injury.[85] Bird *et al.*[86] conducted a randomized controlled double-blind trial of amlodipine in 62 patients with alcoholic hepatitis. The drug was well tolerated, but did not provide any evidence of therapeutic efficacy in these patients.

S-adenosylmethionine

Hepatic deficiency of S-adenosylmethionine, together with elevated serum TNF and lipopolysaccharide (endotoxaemia) are hallmarks of alcoholic liver disease ALD.[87] S-adenosylmethionine deficiency is attributed to its subnormal synthesis, but mechanisms for increased TNF are not known. The deficiency of S-adenosylmethionine may affect the critical balance of pro-inflammatory and anti-inflammatory cytokines. In animal models, S-adenosylmethionine supplementation has been shown to stimulate production of the anti-inflammatory cytokine IL-10. S-adenosylmethionine also dose-dependently decreased LPS-stimulated TNF production from monocytes obtained from patients with alcoholic hepatitis. Clinical trials of S-adenosylmethionine are underway.

Terlipressin and albumin infusion

Hepatorenal syndrome (HRS) is often the critical terminal event in patients with advanced liver disease, including alcoholic hepatitis. Terlipressin, a vasopressin analogue with potent splanchnic vasoconstrictor action, reverses hepatorenal syndrome and improves mortality in patients with cirrhosis.[88–90] In a recent prospective study of 21

cirrhotic patients with HRS, Ortega *et al.*[91] demonstrated that terlipressin combined with albumin infusion led to significant reduction in serum creatinine, a remarkable improvement in circulatory function, including an increase in mean arterial pressure, and suppression of the renin-angiotensin system. Terlipressin, particularly, in combination with albumin infusion, needs to be used in severe alcoholic hepatitis in controlled studies with clear end-points including mortality.

Extracorporeal liver support

Recently there has been increasing interest in the use of extracorporeal albumin dialysis. The use of albumin as dialysate is due to the availability of a large number of binding sites on albumin that have important transport and detoxification functions. In acute liver failure, a large number of endogenous albumin-bound toxins accumulate, and removal of these toxins could lead to improvement in survival. A recent controlled study showed that extracorporeal albumin dialysis improved biochemistry, encephalopathy and 30-day mortality in patients with cirrhosis and superimposed acute liver injury.[92] The molecular adsorbent recirculating system (MARS), is a form of extracorporeal dialysis in which patient's blood is dialysed through an albumin-impregnated membrane. MARS has been shown to be life-saving in patients with severe liver failure of different aetiologies.[93] A recent analysis of data from an international MARS registry suggested an improved survival accompanied by significant improvements of hepatic encephalopathy, mean arterial pressure, serum bilirubin level, creatinine, urea, albumin, INR, ammonia and MELD score. These results have confirmed observations of other trials before which have shown MARS therapy to be an effective and safe extracorporeal liver support in liver failure.[94]

These encouraging results have lead to trials studying role of MARS in severe alcoholic hepatitis. Jalan *et al.*[95] studied the feasibility and efficacy of MARS in eight patients with severe alcoholic hepatitis. The results of this study showed improvement in liver functions, encephalopathy, renal functions and cardiovascular haemodynamics, with apparent survival benefit. As this study was very small, it is difficult to make any comparisons at this time, but use of MARS should be considered as a life-saving measure, and as a bridge to liver transplantation. The authors of this study have started a multicentre, randomized trial. It seems that the MARS device has the potential to improve survival in patients with advanced liver disease, but definitive evidence is lacking at the present time, and it cannot be recommended as a therapy for alcoholic hepatitis outside of clinical trials.

Liver transplantation

Patients with alcoholic liver disease have excellent outcomes after liver transplantation, similar to those for other forms of end-stage chronic liver disease.[96] Tome *et al.*[97] studied the influence of superimposed alcoholic hepatitis on the outcome of liver transplantation in patients with alcoholic cirrhosis. They compared the survival outcomes of liver transplantation in 68 patients transplanted for alcoholic cirrhosis with 101 patients transplanted for various causes. The survival rate of patients with alcoholic hepatitis superimposed on liver cirrhosis was also compared to that of patients with liver cirrhosis alone. Among patients transplanted for alcoholic cirrhosis, survival in 36 patients with superimposed alcoholic hepatitis was similar to that in other 32 patients with liver cirrhosis alone. The study also clearly showed that survival after liver transplantation in patients with alcoholic cirrhosis plus alcoholic hepatitis detected in the explanted liver was similar to that of patients transplanted for non-alcoholic disease.

In the UK, it is usual practice to see patients with alcoholic liver disease abstinent for 6 months prior to transplantation. This is probably a poor indicator of their likelihood of remaining abstinent after transplant, but allows liver recovery so that transplant may not be needed in some patients after all. However, deferring transplantation may not be an option in patients with severe alcoholic hepatitis. Such patients should be discussed with a liver transplant centre. There is almost certainly under-referral of these patients, which serves to obscure a serious shortage of grafts.

Future directions

Significant advances have been made in understanding the pathological mechanisms involved in acute alcoholic hepatitis. In a recent editorial, Day[98] has described these pathological mechanisms in great detail, and has outlined the basis for various prospective anti-apoptotic agents in the treatment of alcoholic hepatitis. Two recent studies[99,100] have demonstrated that hepatocyte apoptosis is a key pathological feature of alcoholic hepatitis. Ziol *et al.*[85] also showed that hepatocyte apoptotic index was related to the severity of alcoholic hepatitis. Hepatic apoptosis could therefore be a potential therapeutic target to treat or to prevent alcoholic

hepatitis in cirrhotic patients. In a murine model of endotoxin-induced liver failure, Z-VAD (a caspase 3-like protease inhibitor) has been shown to attenuate apoptosis and completely prevent hepatocyte necrosis.[101] Anti-apoptotic agents such as Z-VAD need to be tested in human alcoholic hepatitis.

As production of the anti-inflammatory cytokine IL-10 is reduced in alcoholic liver disease, there is potential for role of IL-10 in treating alcoholic hepatitis, perhaps in association with inhibition of TNF. Of the new therapies subjected to proper trials, pentoxiphylline is the most promising. There will be continuing interest in temporary liver support, and extracorporeal albumin dialysis using the MARS device appears to have the most potential. Liver transplantation remains the treatment of choice in patients otherwise dying of liver failure, but patient selection and organ availability remain problematic. In the meantime, corticosteroids have a role, but more research is needed to be able to better select patients who may benefit. Nutritional supplementation is always useful in alcoholic patients who are generally malnourished, and retains a role as an adjunct to medical therapy in alcoholic hepatitis. Perhaps the only certainty for the future is that clinicians will be seeing more of the condition, as there is a shift to heavier and binge drinking, especially among women and the young, and the need for effective treatments has never been greater.

References

1. Hardison WG, Lee FI. Prognosis in the acute liver disease of the alcoholic patients. *N Engl J Med* 1966; **275**:61–66.
2. Pirmohamed M, Brown C, Owens L, Luke C, Gilmore IT, Breckenridge AM, Park BK. The burden of alcohol misuse on inner-city general hospital. *Q J Med* 2000; **93**:291–5.
3. Pirmohamed M, Gilmore IT. Alcohol abuse and the burden on the NHS – time for action. *J R Coll Physicians London* 2000; **34**:161–2.
4. Leevy CM. Cirrhosis in alcoholics. *Med Clinics North Am* 1966; **52**:1445–51.
5. Papanicolaou DA, Wilder RL, Manolagas SC, Chrouso S. The pathophysiologic roles of interleukin-6 in human disease. *Ann Intern Med* 1998; **128**:127–37.
6. Helman RA, Temko MH, Nye SW, Fallon HJ. Alcoholic hepatitis: natural history and evaluation of prednisolone therapy. *Ann Intern Med* 1971; **74**:311–21.
7. Lesesne HR, Bozymski EM, Fallon HJ. Treatment of alcoholic hepatitis and encephalopathy. Comparison of prednisolone and calorie supplements. *Gastroenterology* 1978; **74**:169–73.
8. Maddrey WC, Boitnott JK, Bedine MS, Weber FL Jr, Mezey E, White RI Jr. Corticosteroid therapy of alcoholic hepatitis. *Gastroenterology* 1978; **75**:193–6.
9. Ramond MJ, Poynard T, Rueff B, Mathurin P, Theodore C, Chaput JC. A randomized trial of prednisolone in patients with severe alcoholic hepatitis. *N Engl J Med* 1992; **326**:507–12.
10. Carithers RL, Herlong F, Diehl AM, Shaw EW, Combes B, Fallon HJ, Maddrey WC. Methylprednisolone therapy in patients with severe alcoholic hepatitis. *Ann Intern Med* 1989; **110**:685–90.
11. Mendenhall CL, Anderson S, Garcia-Pont P, Goldberg S, Kiernan T, Seeff LB, Sorrell M, Tamburro C, Weesher R, Zetterman R, et al. Short term and long term survival in patients with alcoholic hepatitis treated with oxandrolone and prednisolone. *N Engl J Med* 1984; **311**:1464–70.
12. Theodossi A, Eddleston ALWF, Williams R. Controlled trial of methylprednisolone therapy in severe acute alcoholic hepatitis. *Gut* 1982; **23**:75–9.
13. Depew W, Boyer T, Omata M, Redekar A, Reynolds T. Double-blind controlled trial of prednisolone therapy in severe acute alcoholic hepatitis and spontaneous encephalopathy. *Gastroenterology* 1980; **78**:524–9.
14. Schumaker JB, Resnick RH, Galambos JT, Makopour H, Iber FL. A controlled trial of methylprednisolone in acute alcoholic hepatitis. *Am J Gastroenterol* 1978; **6969**:443–9.
15. Blitzer BL, Mutchnik MG, Joshi PH, Phillips MM, Fessel JM, Conn HO. Adrenocorticosteroid therapy in alcoholic hepatitis. *Dig Dis Sci* 1977; **22**:477–84.
16. Campra JL, Hamlin EM, Kirshbaum RJ, Olivier M, Redekar AG, Reynolds TB. Prednisone therapy of acute alcoholic hepatitis. *Ann Intern Med* 1973; **79**:625–31.
17. Porter HP, Simon FR, Pope CE, Volwiler W, Fenster LF. Corticosteroid therapy in severe alcoholic hepatitis. *N Engl J Med* 1971; **284**:1250–5.
18. Imperiale TF, McCullough AJ. Do corticosteroids reduce mortality from alcoholic hepatitis? *Ann Intern Med* 1990; **113**:299–307.
19. Poynard T, Ramond MJ, Reuff B, Mathurin P, Theodore C Chaput JC. Corticosteroid therapy reduces mortality from alcoholic hepatitis in patients without encephalopathy. A meta-analysis of randomized trials (RCTs) including French trials. *Hepatology* 1991; **14**:234A.
20. Christensen E, Gluud C. Glucocorticoids are ineffective in alcoholic hepatitis: A meta-analysis adjusting for confounding variables. *Gut* 1995; **37**:113–18.
21. Mathurin P, Mendenhall CJ, Carithers RL Jr, Maddrey WC, Naveau S, Chaput JC, Poynard T. Corticosteroids decrease short-term mortality in patients with severe alcoholic hepatitis: individual data meta-analysis of the last three randomized placebo controlled double-blind trials. *J Hepatol* 2002; **36**:480–7.
22. McClain C, Cohen D. Increased tumour necrosis factor production by monocytes in alcoholic hepatitis. *Hepatology* 1989; **9**:349–51.
23. Bird GL, Sheron N, Goka AK, Alexander GJ, Williams R. Increased plasma tumour necrosis factor in severe alcoholic hepatitis. *Ann Intern Med* 1990; **112**:917–20.
24. McClain CJ, Hill D, Schmidt J, Diehl AM. Cytokines and liver disease. *Semin Liver Dis* 1993; **13**:170–82.
25. Kamimura S, Tsukamoto H. Cytokine gene expression Kupffer cells in experimental alcoholic liver disease. *Hepatology* 1995; **21**:1304–9.
26. Khoruts A, Stahnke L, McClain CJ, Logan G, Allen JI. Circulating tumour necrosis factor, interleukin-1, and

interleukin-6 concentration in chronic alcoholic patients. *Hepatology* 1991; **13**:267–76.

27. Ohlinger W, Dinges HP, Zatlokal K, Mair S, Gollowitsch F, Denk H. Immunohistochemical detection of tumor necrosis factor-alpha, other cytokines and adhesion molecules in human livers with alcoholic hepatitis. *Virchows Arch A Pathol Anat Histopathol* 1993; **423**:169–76.
28. Grove J, Daly A, Bassendine M, Day CP. Association of a tumor necrosis factor polymorphism with susceptibility to alcoholic steatohepatitis. *Hepatology* 1997; **26**:143–6.
29. Allott RL, Quest LJ, Pirmohamed M, Kitteringham NR, Gilmore IT, Park BK. Investigation of the role of TNF α gene polymorphism in alcoholic liver disease. *Hepatology* 1996; **24**:1266A.
30. Hill DB, Marsano L, McClain CJ. Increased plasma interleukin-8 concentrations in alcoholic hepatitis. *Hepatology* 1993; **18**:576–80.
31. Sheron N, Bird G, Kokinas J, Portmann B, Ceska M, Lindley I, Williams R. Circulating and tissue levels of the neutrophil chemotaxin interleukin-8 are elevated in severe alcoholic hepatitis and tissue levels correlate with neutrophil infiltration. *Hepatology* 1993; **18**:41–6.
32. Jalan R, Williams R, Kaser A, Davies N, Zoller H, Hodges S, Graziadei I, Shawcross D, Vogel W, Alisa A, Ludowiczec O, Tilg H. Clinical and cytokine response to anti-TNF antibody therapy in severe alcoholic hepatitis. *Hepatology* 2001; **34**:441A.
33. Spahr L, Rubbia-Brandt L, Frossard J, Giostra E, Pugin J, Fischer M, Egger H, Hadengue A. Combination of steroids with infliximab or placebo in severe alcoholic hepatitis: a randomized controlled pilot study. *J Hepatol* 2002; **37**:448.
34. Strieter R, Remick D, Ward P, Spengler RN, Lynch JP 3rd, Larrick J. Cellular and molecular regulation of tumor necrosis factor-alpha production by pentoxifylline. *Biochem Biophys Res Commun* 1988; **155**:1230–6.
35. Peterson T, Isbrucker R, Hooper M. In vitro effect of platelet-derived growth factor on fibroproliferation and effect of cytokine antagonists. *Immunopharmacology* 2000; **46**:253–61.
36. Zabel P, Schade F, Schalaak M. Inhibition of endogenous TNF formation by pentoxifylline. *Immunobiology* 1993; **187**:1230–6.
37. Neuner P, Klosner G, Pourmojib M, Knobler R, Schwarz T. Pentoxifylline in vivo and in vitro down-regulates the expression of the intercellular adhesion molecule-1 in monocytes. *Immunology* 1997; **90**:435–9.
38. McHutchison JG, Runyon BA, Draguesku JO, Cominelli F, Person JL, Castracane J. Pentoxifylline may prevent renal impairment (hepatorenal syndrome) in severe acute alcoholic hepatitis. *Hepatology* 1991; **14**:96A.
39. 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**:1637–48.
40. Benedetti A, Marucci L. The significance of apoptosis in the liver. *Liver* 1999; **19**:453–63.
41. Kurose I, Higuchi H, Miura S, Saito H, Watanbe N, Hokari R, Hirokawa M, Takaishi M, Zeki S, Nakamura T, Ebinuma H, Kato S, Ishii H. Oxidative stress mediated apoptosis of hepatocytes exposed to acute ethanol intoxication. *Hepatology* 1997; **25**:368–78.
42. Chen Q, Galleano M, Cederbaum AI. Cytotoxicity and apoptosis produced by arachidonic acid in Hep 2G2 c3ells overexpressing human cytochrome P4502EI. *J Biol Chem* 1997; **272**:14532–41.
43. Hug H, Strand S, Grambihler A, Galle J, Hack V, Stremmel W, Krammer PH, Galle PR. Reactive oxygen intermediates are involved in induction of CD95 ligand mRNA expression by cytostatic drugs in hepatoma cells. *J Biol Chem* 1997; **272**:28191–3.
44. Harrison P, Keays R, Bray G, Alexander GJ, Williams R. Improved outcome in paracetamol-induced fulminant hepatic failure following late administration of N-acetylcysteine. *Lancet* 1990; **335**:1572–3.
45. Keays R, Harrison P, Wendon JA, Forbes A, Gove C, Alexander GJ, Williams R. Intravenous N-acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. *Br Med J* 1991; **303**:1026–9.
46. Le Moine O, Evrard S, Eisendrath P, Deschamps C, Deviere J. Treatment of alcoholic hepatitis with intravenous N-acetylcysteine: a pilot trial. *Gastroenterology* 2001; **120(suppl. 1)**:A-545.
47. Forrest EH, Suzuki H, Mackie Helen, *et al.* Relationship of carotenoid and vitamins A and E with the acute inflammatory response in acute alcoholic hepatitis. *Gastroenterology* 2001; **120(suppl. 1)**:A-545.
48. Cox CA, Hespenheide EE, Caldwell SH, *et al.* A single center's experience with acute alcoholic steatohepatitis: Corticosteroids compared to combination ursodeoxycholic acid, vitamin C and vitamin E. *Gastroenterology* 2001; **120(suppl. 1)**:A-545.
49. Phillips M, Curtis H, Portman B, Donaldson N, Bomford A, O'Grady J. Antioxidants versus corticosteroids in the treatment of severe alcoholic hepatitis. *Hepatology* 2001; **34**:250A.
50. Stewart S, Prince M, Bassendine M, Hudson M, James O, Jones D, Record C, Day C. A trial of antioxidant therapy alone or with corticosteroids in acute alcoholic hepatitis. *J Hepatol* 2002; **36(suppl.)**:16.
51. Mendenhall C, Tosch T, Weesner R, Garcia-Pont P, Goldberg S, Kierman T, Seeff LB, Sorell M, Tamburro C, Zetterman R, Miller B, Moore J, Rouster S, Schneider D. VA Cooperative study on alcoholic hepatitis II. Prognostic significance of protein-calorie malnutrition. *Am J Clin Nutr* 1986; **43**:213–18.
52. Calvey H, Davis M, Williams R. Controlled trial of nutritional supplementation, with and without branched chain aminoacid enrichment, in treatment of acute alcoholic hepatitis. *J Hepatol* 1985; **1**:141–51.
53. Kearns PJ, Young H, Garcia G, Blaschke T, O'Hanlon G, Rinki M, Sucher K, Gregory P. Accelerated improvement of alcoholic liver disease with enteral nutrition. *Gastroenterology* 1992; **102**:200–5.
54. Cabre E, Gonzalez-Huix F, Abad-Lacruz A, Esteve M, Acero D, Fernandez-Benares F, Xiol X, Gassull MA. Effect of total enteral nutrition on the short-term outcome of severely malnourished cirrhotics – A randomized controlled trial. *Gastroenterology* 1990; **99**:1192–3.
55. Cabre E, Rodrriguez-Iglesias P, Caballeria J, Quer JC, Sanchez-Lombrana JL, Pares A, Papo M, Planas R, Gassull MA, and The Spanish Group for the Study of Alcoholic Hepatitis. 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.

56. Diehl AM, Beitnott JK, Herlong HF, Potter JJ, Van Duyn MA, Chandler E, Mezey E. Effect of parenteral aminoacid supplementation in alcoholic hepatitis. *Hepatology* 1985; **5**:57–63.
57. Nasrallah SM, Galambos JT. Aminoacid therapy of alcoholic hepatitis. *Lancet* 1980; **2**:1276–7.
58. Naveau S, Pelletier G, Poynard T, Attali P, Poitrine A, Buffet C, Etienne JP, Chaput JC. A randomized clinical trial of supplementary parenteral nutritionin jaundiced alcoholic cirrhotic patients. *Hepatology* 1986; **6**:270–4.
59. Achord JL. A prospective randomized clinical trial of peripheral aminoacid–glucose supplementation in acute alcoholic hepatitis. *Am J Gastroenterol* 1987; **82**:871–5.
60. Simon D, Galambos JT. A randomized controlled study of peripheral parenteral nutrition in moderate and severe alcoholic hepatitis. *J Hepatol* 1988; **7**:200–7.
61. Mezey E, Caballeria J, Mitchell MC, Pares A, Herlong HF, Rodes J. Effect of parenteral amino acid supplementation on short-term and long-term outcomes in severe alcoholic hepatitis: reandomized controlled trial. *Hepatology* 1991; **14**:1090–6.
62. Mendenhall C, Moritz T, Roselle GA, Morgan TR, Nemchauskey BA, Tamburro CH, Schiff ER, McClain CJ, Marsano LS, Allen JI. A study of oral nutritional support with oxandrolone in malnourished patients with alcoholic hepatitis: results of a Department of Veterans Affairs Cooperative Study. *Hepatology* 1993; **17**:564–76.
63. Rambaldi A, Iaquinto G, Gluud C. Anabolic-androgenic steroids for alcoholic liver disease. A Cochrane review. *Am J Gastroenterol* 2002; **97**:1674–81.
64. Israel Y, Videla L, MacDonald A. Metabolic alteration produced in by chronic ethanol administration: comparison between the effects produced by ethanol and by thyroid hormones. *Biochem J* 1973; **134**:523–9.
65. Bernstein J, Videla L, Israel Y. Hormonal influences in the development of the hypermetabolic state of the liver produced by chronic administration of ethanol. *J Pharmacol Experiment Therap* 1975; **192**:583–91,.
66. Israel Y, Kalant H, Orrego H, Khanna JM, Videla L, Phillips JM. Experimental alcohol-induced hepatic necrosis: suppression by propylthiouracil. *Proc Nat Acad Sci* 1975; **72**:1137–41.
67. Orrego H, Kalant H, Israel Y, Blake J, Medline A, Rankin JG, Armstrong A, Kapur B. Effect of short term therapy with PTU in patients with alcoholic liver disease. *Gastroenterology* 1979; **76**:105–15.
68. Halle P, Pare P, Kaptein E, Kanel G, Redekar AG, Reynolds TB. Double blind, controlled trial of propylthiouracil in patients with severe alcoholic hepatitis. *Gastroenterology* 1982; **87**:925–31.
69. Peirrugues R, Blanc P, Barneon C. Short-term therapy with propylthiouracil for alcoholic hepatitis. A clinical, biochemical and histological randomized trial. *Gastroenterology* 1989; **96**:A644.
70. Serrano-Cancino H, Botero R, Jeffers L. Treatment of severe alcoholic hepatitis with propylthiouracil (abstract). *Am J Gastroenterol* 1981; **76**:194.
71. Rambaldi A, Gluud C.Meta-analysis of propylthiouracil for alcoholic liver disease–a Cochrane Hepato-Biliary Group Review. *Liver* 2001; **21**:398–404.
72. Malawitsa SE. The action of colchicine in gouty arthritis. *Arthritis Rheum* 1975; **18(suppl. 6)**:835–46.
73. Poo JL, FeldmannG, Moreau A, Gaudin C, Lebrec D. Early colchicine administration reduces hepatic fibrosis and portal hypertension in rats with bile duct ligation. *J Hepatol* 1993; **19**:90–4.
74. Trinchet JC, Beaugrand M, Callard P, Hartmann DJ, Gotheil C, Nusgens BV, Lapiere CM, Ferrier JP. Treatment of alcoholic hepatitis with colchicine: results of a randomized double-blind trial. *Gastroenterol Clin Biol* 1989; **13**:551–5.
75. Akriviadis EA, Steindel H, Pinto PC, Fong TL, Kanel G, Reynolds TB, Gupta S. Failure of colchicine to improve short-term survival in patients with alcoholic hepatitis. *Gastroenterology* 1990; **99**:811–18.
76. Nimni ME, Bavetta LA. Collagen defect induced by penicillamine. *Science* 1965; **150**:905–7.
77. Resnick RH, Boitnott J, Iber FL, Makopour H, Cerda JJ. Preliminary observation of D-penicillamine therapy in acute alcoholic liver disease. *Digestion* 1974; **11**:257–65.
78. Fang JW, Bird GL, Nakamura T, Davis GL, Lau JY. Hepatocyte proliferation as an indicator of outcome in alcoholic hepatitis. *Lancet* 1994; **343**:820–3.
79. Baker, Bucher NLR, Swaffield MN. Regulation of hepatic regeneration in rats by synergistic action of insulin and glucagon. *Proc Nat Acad Sci USA* 1975; **72**:1157–60.
80. Baker AL, Jaspan JB, Hains NW, Hatfield GE, Krager PS, Schneider JF. A randomized clinical trial of insulin and glucagon infusion for treatment of alcoholic hepatitis: progress report. *Gastroenterology* 1981; **80**:1410–14.
81. Feher J, Cornides A, Romany A, Karteszi M, Szaky L, Gogl A, Picazo J. A prospective multicenter study of insulin and glucagon infusion in acute alcoholic hepatitis. *J Hepatol* 1997; **5**:224–31.
82. Trinchet JC, Balkau B, Poupon RE, Heintzmann F, Callard P, Gotheil C, Grange JD, Velter D, Pauwels A, Labadie H. Treatment of severe alcoholic hepatitis by insulin and glucagon infusion: a multicenter sequential trial. *Hepatology* 1992; **15**:76–81.
83. Bird GL, Lau JY, Koskinas J, Wicks C, Williams R. Insulin and glucagon infusion in acute alcoholic liver disease: a prospective randomized controlled trial. *Hepatology* 1991; **14**:1097–101.
84. Radvan G, Kanel G, Redeker A. Insulin and glucagon infusion in acute alcoholic hepatitis. *Gastroenterology* 1982; **82**:A1154.
85. Iimuro Y, Ikejima K, Rose ML, Bradford BU, Thurman RG. Nimodipine, a dihydropyridine-type calcium channel blocker, prevents alcoholic hepatitis caused by chronic intragastric ethanol exposure in rat. *Hepatology* 1996; **24**:2207–11.
86. Bird GL, Prach AT, McMahon AD, Forrest JA, Mills PR, Danesh BJ. Randomized controlled double-blind trial of the calcium channel antagonist amlodipine in treatment of acute alcoholic hepatitis. *J Hepatol* 1998; **28**:194–8.
87. McClain CJ, Hill DB, Song Z, Chawla R, Watson WH, Chen T, Barve S. S-Adenosylmethionine, cytokines, and alcoholic liver disease. *Alcohol* 2002; **27**:185–92.
88. Alessandria C, Venon WD, Marzano A, Barletti C, Fadda M, Rizzetto M. Renal failure in cirrhotic patients: role of terlipressin in clinical approach to hepato-renal syndrome type2. *Eur J Gastroenterol Hepatol* 2002; **14**:1363–8.
89. Moreau R, Durand F, Poynard T, Duhamel C, Cervoni JP, Ichai P, Abergel A, Halimi C, Pauwels M, Bronowicki JP, Giostra E, Fleurot C, Gurnot D, Nouel O, Renard P, Rivoal M,

Blanc P, Coumaros D, Ducloux S, Levy S, Pariente A, Perarnau JM, Roche J, Scribe-Outtas M, Valla D, Bernard B, Samuel D, Butel J, Hadengue A, Platek A, Lebrec D, Cadranel JF. Terlipressin in patients with cirrhosis and type 1 hepatorenal syndrome: a retrospective multicenter study. *Gastroenterology* 2002; **122**:923–30.

90. Colle I, Durand F, Pessione F, Rassiat E, Bernuau J, Barriere E, Lebrec D, Valla DC, Moreau R. Clinical course, predictive factors and prognosis in patients with cirrhosis and type 1 hepatorenal syndrome treated with Terlipressin: a retrospective analysis. *J Gastroenterol Hepatol* 2002; **17**:882–8.
91. Ortega R, Gines P, Uriz J, Cardenas A, Calahorra B, De Las Heras D, Guevara M, Bataller R, Jimenez W, Arroyo V, Rodes J. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective, nonrandomized study. *Hepatology* 2002; **36**:941–8.
92. Heemann U, Treichel U, Loock J, Pholipp T, Gerken G, Malago M, Loehr M, Liebe S, Mitzner S, Schmidt R, Stange J. Albumin dialysis in cirrhosis with superimposed acute liver injury: A prospective controlled study. *Hepatology* 2002; **36**:949–958.
93. Wilmer A, Nevens F, Evenepoel P, Hermans G, Fevery J. The Molecular Adsorbent Recirculating System in patients with severe liver failure: clinical results at the K.U. Leuven. *Liver* 2002; **22 (Suppl. 2)**:52–5.
94. Steiner C, Mitzner S. Experiences with MARS liver support therapy in liver failure: analysis of 176 patients of the International MARS registry. *Liver* 2002; **22(Suppl. 2)**:20–5.
95. Jalan R, Sen S, Steiner C, Kapoor D, Alisa A, Williams R. Extracorporeal liver support with molecular adsorbents recirculating system in patients with severe acute alcoholic hepatitis. *J Hepatol* 2003; **38**:24–31.
96. Bellamy CO, DiMartini AM, Ruppert K, Jain A, Dodson F, Torbenson M, Starzl TE, Fung JJ, Demetris AJ. Liver transplantation for alcoholic cirrhosis: long term follow-up and impact of disease recurrence. *Transplantation* 2001; **72**:619–26.
97. Tome S, Martinez-Rey C, Gonzalez-Quintela A, Gude F, Brage A, Otero E, Abdulkader I, Forteza J, Bustamante M, Varo E. Influence of superimposed alcoholic hepatitis on the outcome of liver transplantation for end-stage alcoholic liver disease. *J Hepatol* 2002; **36**:793–8.
98. Day CP. Apoptosis in alcoholic hepatitis: a novel therapeutic agent? *J Hepatol* 2001; **34**:330–3.
99. Ziol M, Tepper M, Lohez M, Arcangeli G, Ganne N, Christidis C, Trinchet JC, Beaugrand M, Guillet JG, Guettier C. Clinical and biological relevance of hepatocyte apoptosis in alcoholic hepatitis. *J Hepatol* 2001; **34**:254–60.
100. Natori S, Rust C, Stadheim LM, Srinivasan A, Burgart LJ, Gores GJ. Hepatocyte apoptosis is a pathologic feature of human alcoholic hepatitis. *J Hepatol* 2001; **34**: 248–53.
101. Jaeschke H, Fisher MA, Lawson JA, Simmons CA, Farhood A, Jones DAl. Activation of caspase 3(CPP32)-like proteases is essential for TNF-α induced hepatic parenchymal apoptosis and neutrophil-mediated necrosis in a murine endotoxin shock model. *J Immunol* 1998; **160**:3480–6.