The management of alcoholic hepatitis

Alcoholic hepatitis is an increasingly common reason for hospital admission which carries a high mortality. This review describes a clinical approach to the definition, assessment and management of this condition.

Death from alcohol misuse in the UK has been increasing, and in Scotland has increased by 236% between 1980 and 2002 (National Alcohol Information Resource, 2004). Alcohol-related liver disease accounts for the majority of these deaths (Baker and Rooney, 2003). While many patients presenting with alcoholic liver disease will have cirrhosis, as many as 60% may have evidence of alcohol-related hepatitis (Hislop et al, 1983). Alcoholic hepatitis is the most florid manifestation of alcohol-related liver disease, but has the potential for reversibility, and therefore treatment. It is a common reason for acute medical admission and has a 28-day mortality of up to 60% (Morgan, 1992). However, there is considerable debate regarding the diagnosis of this condition and little consensus on its management. This has led to uncertainty regarding the management of this increasingly common life-threatening condition. This article is a clinically driven approach to alcoholic hepatitis.

Diagnosis of alcoholic hepatitis

In view of its importance, it may seem odd that there should be some debate regarding the diagnosis of alcoholic hepatitis. To the pathologist there are pathognomic features that suggest alcoholic hepatitis. These include a steatohepatitis often with Mallory bodies, an associated neutrophil infiltrate, and damage most apparent around the central veins (zone 3). However, these appearances are not disease specific as identical features may be seen in non-alcoholic steatohepatitis. However, with a compatible history and biochemical picture, histology is the 'gold standard' for diagnosis of alcoholic hepatitis. Although these features are indicative of alcoholic hepatitis, there are no internationally recognized histological criteria for diagnosis.

In addition there are problems with obtaining histology in the clinical setting. The presence of ascites and/or a coagulopathy will often contraindicate percutaneous liver biopsy. Performing a transjugular liver biopsy can minimize these risks, but the appropriate expertise may not be immediately available. Thus histology may not be immediately obtainable and relying on it for diagnosis may result in delay before appropriate management can be instituted.

Alcoholic hepatitis to the clinician is different from that recognized by the pathologist. Most clinicians would suspect alcoholic hepatitis with the onset of jaundice in a patient with a history of recent significant alcohol excess. There may be other manifestations of decompensated liver disease such as ascites and encephalopathy. It is here that the pathological features and the clinical features of alcoholic hepatitis diverge. In one study only 65% of patients with histological evidence of alcoholic hepatitis were jaundiced and only 5% had signs of encephalopathy (Hislop et al, 1983).

So the practical clinical question is whether the diagnosis of alcoholic hepatitis can be made without a biopsy? An accuracy of about 80% has been quoted for the clinical diagnosis of alcoholic hepatitis when compared with histology. This is certainly true in studies that rely on the modified discriminant function or loose clinical features as diagnostic criteria (Mendenhall et al, 1984; Ramond et al, 1992). However, if only those studies with a minimum level of bilirubin as a criterion for diagnosis are looked at, the accuracy rises to nearly 100% (Phillips et al, 2006). Therefore it seems possible to determine criteria for the diagnosis of clinically relevant alcoholic hepatitis without reliance on histology. These are: a history of excessive alcohol ingestion, serum bilirubin >80 μmol/litre, aspartate aminotransferase <500 iu (or alanine aminotransferase <300 iu), and exclusion of autoimmune, acute viral, obstructive biliary or malignant liver disease. Characteristic features of alcoholic hepatitis (but not necessary for diagnosis) include pyrexia, hepatomegaly, a hepatic bruit, ascites, encephalopathy, an aspartate aminotransferase:alanine aminotransferase ratio >1.5, and peripheral leucocytosis. It should be noted, however, that as alcohol misuse is increasingly prevalent, alcoholic hepatitis may co-exist with other liver conditions, particularly chronic hepatitis C infection.

While nearly all patients who fulfil these criteria will have features of alcoholic hepatitis on biopsy, approximately 50–60% will also have severe fibrosis or cirrhosis. There is no evidence that co-existing cirrhosis worsens the short-term outcome of patients with alcoholic hepatitis, indicating that the acute inflammatory process is primarily responsible for the poor short-term prognosis of these patients (Rincon et al, 2007). The presence of cirrhosis (confirmed or suspected) should therefore not prevent consideration of specific treatment for alcoholic hepatitis.

Assessment of severity

A clinical diagnosis of alcoholic hepatitis still encompasses a wide spectrum of disease. Assessment of the severity of alcoholic hepatitis is vital not only to identify

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those patients with a poor prognosis, but also to target treatment effectively. In 1989 a discriminant function was modified in the context of a placebo-controlled corticosteroid trial involving 66 patients (Carithers et al, 1989). A modified discriminant function of >32 and/or the presence of encephalopathy in placebo-treated patients was associated with a 65% 28-day survival. A re-analysis of a previously published placebo-controlled corticosteroid trial confirmed this observation with a 68% 28-day survival in placebo-treated patients with a discriminant function ≥32, while those with a score <32 had a 28-day survival of 93% (Mathurin et al, 2002) (*Table 1*).

However, there is doubt about the usefulness of the discriminant function. The Glasgow Alcoholic Hepatitis Score (*Table 2*) has been described for the assessment of patients presenting with a clinical diagnosis of alcoholic hepatitis (Forrest et al, 2005). Five variables were identified of predictive value for 28- and 84-day outcome: age, serum bilirubin level, prothrombin time ratio or international normalized ratio, peripheral white cell count, and blood urea level. This score was validated in a separate cohort of 195 patients from throughout the UK. The Glasgow Alcoholic Hepatitis Score appears to be accurate irrespective of whether the international normalized ratio or the prothrombin time ratio is used, and does not rely on creatinine, the measurement of which may be inaccurate in the presence of hyperbilirubinaemia (Lolekha and Sritong, 1994). The Glasgow Alcoholic Hepatitis Score is more specific for mortality and had a greater overall accuracy than the discriminant function. In addition, a Glasgow Alcoholic Hepatitis Score ≥9 may identify patients most likely to benefit from corticosteroid treatment (see below).

The Model of End-stage Liver Disease has been advocated in the assessment of alcoholic hepatitis. The Model of End-stage Liver Disease score itself has never been shown to be statistically superior to the discriminant function (Sheth et al, 2002; Soultati et al, 2006). In addition, the threshold, or optimal cut-point, of Model of End-stage Liver Disease score for identifying patients with a poor prognosis varies widely between published studies, from 11 to 30.5 depending upon the timing of the score calculation, the version of Model of End-stage Liver Disease score used and the end-point studied.

The Lille score has been used to identify patients with a poor prognosis (Louvet et al, 2007). While this is an accurate score, it relies on the evolution of bilirubin during the first week of corticosteroid treatment, thus it is more a marker of treatment response than an immediate assessment of likely outcome. In this regard it does not describe the natural history of disease, nor does it inform the need for therapeutic intervention as this decision has already been taken. Another score, ABIC (age, bilirubin, international normalized ratio, creatinine), has been advocated using similar variables to the Glasgow Alcoholic Hepatitis Score minus the white cell count (Dominguez et al, 2008). This has yet to be tested in other patient populations and has not been shown to inform the decision to treat these patients.

Management of alcoholic hepatitis

General management

All patients with alcoholic hepatitis irrespective of severity require a minimum standard of care. Patients are at risk of sepsis and indeed the clinical features of alcoholic hepatitis can resemble those of the sepsis syndrome. Close vigilance for sepsis and a low threshold for the use of antibiotics are required. In addition patients with alcoholic hepatitis often have significant protein-energy malnutrition. Nutritional support is vital for these patients. Several randomized trials have explored the use of parenteral and enteral nutritional support in alcoholic hepatitis (Morgan, 1996). The methodology of these studies has been variable and a clear improvement in survival has not been demonstrated. However, there has been surrogate evidence of benefit with improvements in liver blood tests. In general, patients who fail to achieve a positive nitrogen balance have a higher mortality. One study has suggested that enteral nutrition may be as useful as corticosteroid treatment in patients with a discriminant function >32 (Cabre et al, 2000). However, this study used a specific formulation of feed ('hepatical')

Table 1. Scoring systems used in the assessment of alcoholic hepatitis

Scoring system	Formula
Discriminant function	(4.6 x PT) + serum bilirubin (mg/dl)
Modified discriminant function	4.6 ($PT_{patient} - PT_{control}$) + serum bilirubin (µmol/litre)/17.1
Model of End-stage Liver Disease score	3.8 x $\log_e$(bilirubin, mg/dl) + 11.2 x $\log_e$(INR) + 9.6 x $\log_e$(creatinine, mg/dl)
Lille score	3.19 – (0.101 x age in years) + (0.147 x albumin day 0 in g/litre) + (0.0165 x evolution in bilirubin level in µM) – (0.206 x renal insufficiency*) – (0.0065 x bilirubin day 0 in µM) – (0.0096 x INR) Lille score = EXP(-R) / [1+EXP(-R)]
ABIC score	(age x 0.1)+(bilirubin x 0.08)+(creatinine x 0.3)+(INR x 0.8)

*creatinine>115 µM. ABIC = age, bilirubin, international normalized ratio, creatinine; EXP = exponential function; INR = international normalized ratio; PT = prothrombin time.

Table 2. The Glasgow Alcoholic Hepatitis Score

Score given	1	2	3
Age	<50	≥50	–
White blood cell count (10^9/litre)	<15	≥15	–
Urea (mmol/litre)	<5	≥5	–
Prothrombin time ratio or international normalized ratio	<1.5	1.5–2.0	>2.0
Bilirubin (µmol/litre)	<125	125–250	>250

which has a unique balance of fatty acids and amino acids. It is unclear whether standard off the shelf enteral nutrition formulations might have the same disease-specific benefit. However, nutritional support forms a vital component of the management of alcoholic hepatitis irrespective of what other treatments are used.

Specific treatments

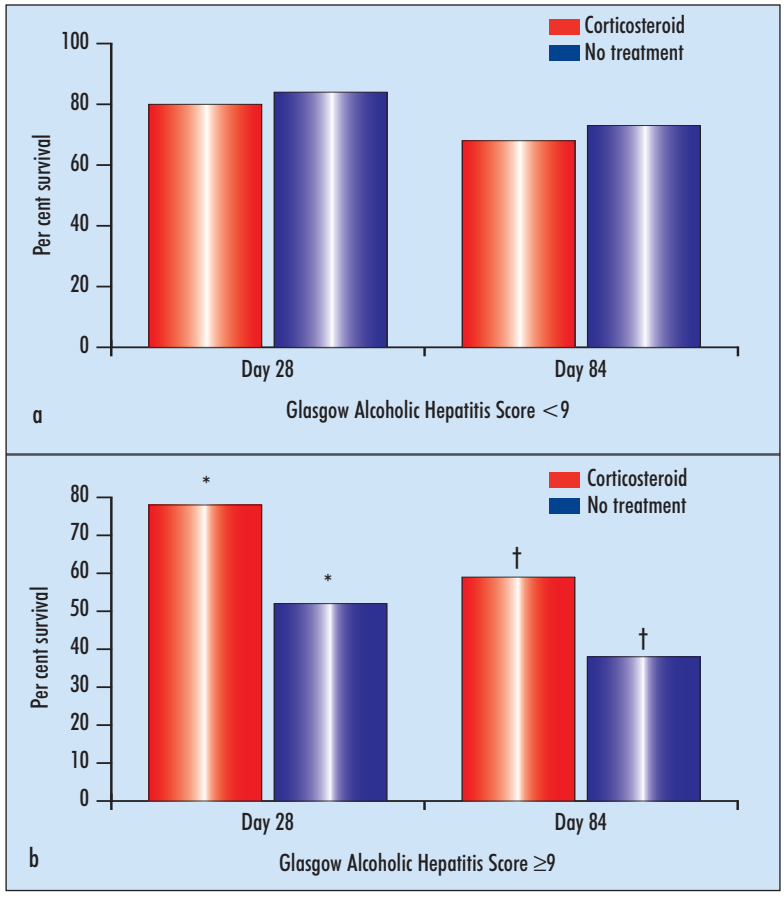
Corticosteroids

Since 1971 there have been at least 13 randomized studies and four meta-analyses investigating the role of corticosteroid therapy for this condition (Morgan, 1996). Despite this apparent wealth of evidence, controversy persists. The inclusion criteria for these trials varied widely and the results were equally variable. None of these studies had adequate statistical power to make a statement with 80% confidence. However, a re-analysis of three randomized controlled trials, only including patients with a discriminant function >32, seems to indicate a significant benefit from corticosteroid therapy (Mathurin et al, 2002). Patients treated with corticosteroids had a 28-day survival of 84.6% compared with 65.1% for placebo-treated patients (P=0.001). Advocates for corticosteroids cite significant improvement in the short- to medium-term mortality, while detractors cite the risks of potentiating sepsis and gastrointestinal haemorrhage with steroid therapy. The most recent meta-analysis was reported overall as negative. However, subgroup analysis of the best designed trials and those that had stringent entry criteria (discriminant function >32 and/or encephalopathy) did show an improved survival with corticosteroids (Rambaldi et al, 2008). The current recommendations of the American College of Gastroenterology suggest corticosteroid use for the treatment of acute alcoholic hepatitis in severe disease as indicated by a discriminant function of >32 (McCullough and O'Connor, 1998).

The Glasgow Alcoholic Hepatitis Score may also identify patients who may benefit from corticosteroid treatment. In a retrospective analysis of patients with a discriminant function ≥32, patients with a Glasgow Alcoholic Hepatitis Score <9 did not benefit from corticosteroid treatment. However, for patients with a Glasgow Alcoholic Hepatitis Score ≥9, the 28-day survival for untreated and corticosteroid-treated patients was 52% and 78% (P=0.002) and 84-day survival 38% and 59% (P=0.02) respectively (*Figure 1*) (Forrest et al, 2007). This suggests that as a more specific indicator of severe disease, the Glasgow Alcoholic Hepatitis Score is more able to identify patients who will benefit from corticosteroid treatment (*Figure 2*).

Corticosteroids can induce a rapid fall in serum bilirubin levels compared to placebo-treated patients, and this fall is associated with a survival benefit. One study demonstrated that patients with a fall in bilirubin after 1 week of treatment had a 6-month survival of 82.8% compared with 23% for those without a fall in bilirubin (P=0.00001) (Mathurin et al, 2003). This has been followed up by the same group with the Lille score. This score uses a range of variables including the change in bilirubin after 1 week of treatment to create a prognostic score (Louvet et al, 2007). In a smaller retrospective study the author observed dramatic responses to corticosteroids among some, but not all, patients with severe acute alcoholic hepatitis (Morris and Forrest, 2005). In this study group demonstration of a 25% reduction in serum bilirubin at approximately 1 week was associated with a substantial and sustained reduction in mortality.

Figure 1. Effect of corticosteroids and pentoxifylline upon survival relative to Glasgow Alcoholic Hepatitis Score. a. Survival at day 28 and day 84 in patients with a discriminant function ≥32 and a Glasgow Alcoholic Hepatitis Score <9, relative to the Glasgow Alcoholic Hepatitis Score and corticosteroid treatment. b. Survival at day 28 and day 84 in patients with a discriminant function ≥32 and a Glasgow Alcoholic Hepatitis Score ≥9, relative to the Glasgow Alcoholic Hepatitis Score and corticosteroid treatment. * P<0.002 (26% difference, 95% confidence interval = 11–41%) cf no treatment. † P<0.02 cf no treatment (21% difference, 95% confidence interval = 5–37%). From Forrest et al (2007).



Pentoxifylline

Pentoxifylline has also been studied in the treatment of alcoholic hepatitis in one randomized controlled trial (Akriviadis et al, 2000). Pentoxifylline is believed to act by inhibiting tumour necrosis factor-alpha (TNF-α). This study used the rather indistinct end-point of survival during the index hospitalization. The overall mor-

tality was 24.5% in the pentoxifylline group compared with 46.1% in the placebo-treated group (P=0.037 on an intention-to-treat basis; P=0.09 on a per-protocol basis). Deaths from hepatorenal syndrome were significant in the pentoxifylline-treated group (50%) compared with placebo (91.7%; P=0.009). However, nearly one quarter of patients treated with pentoxifylline had to stop treatment because of side effects.

Corticosteroids or pentoxifylline

Only one study has so far been published comparing corticosteroid and pentoxifylline treatment, and no studies have examined the combination of these two treatments. The single small comparative study has suggested an improved survival with pentoxifylline with again a lesser incidence of hepatorenal failure (no patients in the pentoxifylline group and six out of 34 in the corticosteroid-treated group) (Krishna et al, 2009). However, the numbers studied are small and the role for pentoxifylline, while promising, remains to be clarified.

Specific anti-TNF-α therapies

TNF-α is believed to be pivotal in the pathogenesis of alcoholic hepatitis. Certainly soluble TNF receptor concentrations have been shown to correlate with severity (Spahr et al, 2004). To investigate the possible use of TNF-α antagonism a randomized controlled study was established with all patients treated with steroids but randomized to a high dose, high intensity infliximab regimen (10 mg/kg on three occasions; week 0, 2, and 4) (Naveau et al, 2004). The study was discontinued prematurely as there was excess mortality in the infliximab group. However, more recently a small (n=19) uncontrolled study has again suggested benefit with this treatment with a more modest regimen (single dose 5 mg/kg infliximab) (Sharma et al, 2009). Another controlled study investigated the use of etanercept in alcoholic hepatitis. However, this again was a negative study (Boetticher et al, 2008). It is possible that the anti-inflammatory benefits of TNF-α antagonism are negated by the anti-regenerative effects of this treatment. At present the use of TNF-α antagonists in alcoholic hepatitis cannot be advocated without strictly controlled studies.

Rescue treatment for non-responders

For those who respond to corticosteroids (however that may be defined) the short-term prognosis is good. However, for those without such a response the outlook is poor. The use of pentoxifylline as treatment for non-responders has been studied (Louvet et al, 2008). No survival benefit was seen with such rescue treatment. In particular there was no reduction in the incidence of renal failure with pentoxifylline treatment in this group of patients. At present there is no clear therapeutic strategy for these non-responders other than continued supportive treatment.

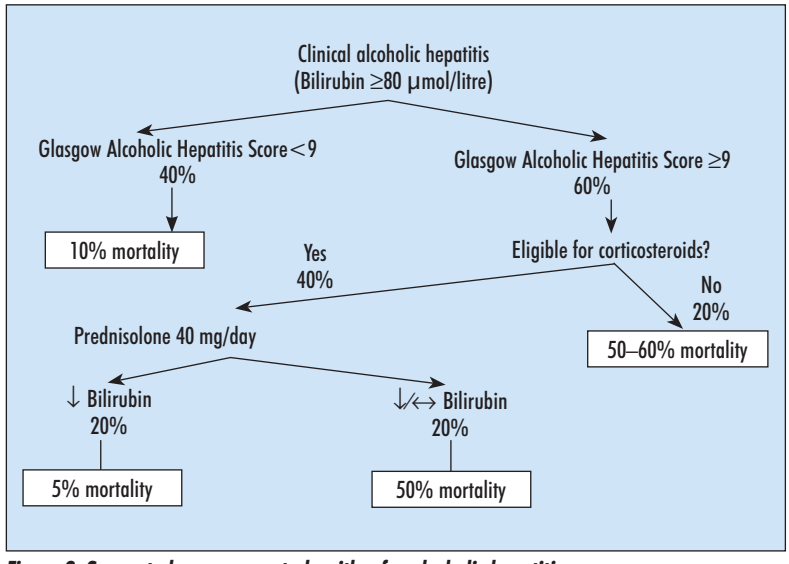


Figure 2. Suggested management algorithm for alcoholic hepatitis.

Alcoholic hepatitis and sepsis

Many patients do not receive specific treatment for alcoholic hepatitis. All the randomized controlled studies of corticosteroids and the single study of pentoxifylline have excluded patients with evidence of active sepsis. Clinicians are reluctant to prescribe specific treatment for alcoholic hepatitis in this context. However, such concerns may not be warranted as increasingly corticosteroids are used routinely for septic shock in the critically ill (Annane et al, 2009). A study looked at the use of hydrocortisone 200 mg/day in patients with cirrhosis septic shock who had evidence of relative adrenocortical insufficiency (based on a short synacthen test) (Fernandez et al, 2006). The majority of these patients had alcoholic liver disease and 40% had 'active alcoholism' (possibly indicating co-existent alcoholic hepatitis). Mortality and refractory shock were much less frequent in treated patients compared with historical controls.

Pentoxifylline has also been studied in the context of sepsis. Two studies in adult patients with severe sepsis in intensive care settings have indicated beneficial effects with pentoxifylline (Staubach et al, 1998). There were improvements in scores of multi-organ dysfunction and advantageous changes in haemodynamic parameters. However, so far the published studies of pentoxifylline in alcoholic hepatitis have specifically excluded patients with active sepsis.

It is possible, therefore, that the perceived risks of corticosteroids and pentoxifylline in active or recent sepsis may not be as great as generally accepted. This can only be clarified by performing randomized studies in this difficult group of patients with both sepsis and alcoholic hepatitis.

Conclusions

The study and management of alcoholic hepatitis has been fraught by disagreement regarding its diagnosis, assessment and treatment. For progress to be made, con-

sensus is required on a clinical definition of alcoholic hepatitis not reliant on pathological criteria, and on a universally applicable score of severity. Patients with alcoholic hepatitis require nutritional support and surveillance for sepsis. Patients with severe disease (discriminant function ≥32, or more specifically Glasgow Alcoholic Hepatitis Score ≥9) may benefit from corticosteroids, or perhaps pentoxifylline. Patients with concomitant sepsis, or who are unresponsive to corticosteroids, remain problematic and have a high mortality. Further studies are needed for these groups of patients. However, for those patients with sepsis, broadening the indications for corticosteroids and/or pentoxifylline may be beneficial. BJHM

Conflict of interest: none.

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KEY POINTS

- Alcoholic hepatitis is the most florid manifestation of alcohol-specific liver disease with a short-term mortality of up to 60%.
- Biopsy provides a 'gold standard' for diagnosis of alcoholic hepatitis, but a clinical diagnosis can be made with confidence in patients with significant jaundice, typical laboratory features and the absence of other forms of liver disease.
- Severe disease is defined as a discriminant function >32, or more specifically a Glasgow Alcoholic Hepatitis Score ≥9.
- All patients with alcoholic hepatitis should be considered for nutritional support and there should be a low threshold for the treatment of sepsis.
- Patients with severe disease should be considered for specific treatment with corticosteroids or perhaps pentoxifylline.
- Patients who fail to respond to corticosteroids in the first week of treatment have an extremely poor prognosis.

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