A clinical approach to alcoholic hepatitis

EH Forrest
Consultant Hepatologist, Department of Gastroenterology, Glasgow Royal Infirmary, Glasgow, Scotland

ABSTRACT There has been a dramatic increase in alcoholic liver disease in Scotland over recent years. Alcoholic hepatitis is perhaps the most florid manifestation of this, however considerable controversy exists regarding its diagnosis and management. This review indicates that it is possible to confidently make a diagnosis of alcoholic hepatitis on clinical grounds using a minimum threshold of serum bilirubin as a diagnostic criterion. All patients with alcoholic hepatitis need nutritional assessment and support. The severity of alcoholic hepatitis can be ascertained using the Discriminant Function, however the Glasgow Alcoholic Hepatitis Score appears to be more specific and accurate predictor of outcome. Patients with severe disease should be considered for specific treatment. The evidence is in favour of corticosteroids which have the added benefit of allowing responsiveness to the treatment to be assessed after one week. Pentoxifylline may be a useful alternative to corticosteroids. The patients with alcoholic hepatitis and concomitant sepsis have a very poor prognosis. Previously regarded as a contraindication to specific treatment, it might be beneficial to broaden the indications for corticosteroids or pentoxifylline in these patients.

KEYWORDS Alcoholic hepatitis, corticosteroids, Pentoxifylline

LIST OF ABBREVIATIONS Alanine aminotransferase (ALT), aspartate aminotransferase (AST), Discriminant Function (DF), non-alcoholic steatohepatitis (NASH), modified Discriminant Function (mDF), Glasgow Alcoholic Hepatitis Score (GAHS), International Normalised Ratio (INR), Model of End-stage Liver Disease (MELD), prothrombin time (PT)

DECLARATION OF INTERESTS No conflict of interests declared.

Alcohol related mortality in Scotland has increased by 236% between 1980 and 2002. Alcohol related liver disease accounts for many of these deaths. Whilst many patients presenting with alcoholic liver disease will have cirrhosis, more than 60% will have evidence of an alcohol related hepatitis. Alcoholic hepatitis is the most florid manifestation of alcoholic related liver disease, but is potentially reversible. It is widely appreciated as being a common reason for acute medical admission and recognised to have a 28 day mortality of up to 60%. However there exists considerable debate regarding the diagnosis of this condition and little consensus upon its management. The following article is not a systematic review, but rather a description of a clinical approach to this condition.

WHAT IS ALCOHOLIC HEPATITIS?

In view of the importance of this diagnosis, this may seem an odd question. However the answer to the question depends upon who you are. To a pathologist the answer is quite simple. The pathognomonic features of alcoholic hepatitis are a steatohepatitis often with Mallory bodies. There is an associated neutrophil infiltrate and the damage is most apparent around the central veins (zone 3). These appearances are not entirely specific as identical features are seen in NASH. However with a compatible history and biochemical picture, histology is the 'gold standard' for diagnosis of alcoholic hepatitis.

However there are problems with obtaining histology in the clinical setting. The presence of ascites and/ or a coagulopathy will often contraindicate percutaneous liver biopsy. A clinical approach to alcoholic hepatitis

Vomiting 45%
Hepatomegaly 86%
Splenomegaly 7%
↑ AST 85%
↑ Bilirubin 65%
↑ Alk Phos 64%
↑ γGT 91%
↑ WCC 29%
↓ Albumin 48%
Ascites 28%
Encephalopathy 5%

TABLE 1 Clinical and laboratory associations of biopsy-proven alcoholic hepatitis.
biopsy. These risks can be minimised by performing a transjugular liver biopsy, but the appropriate expertise may not be immediately available. Thus, histology may not be obtainable, or reliance upon it for diagnosis may result in delay before appropriate management can be instituted.

Alcoholic hepatitis to the clinician is different to that of the pathologist. Most clinicians would suspect alcoholic hepatitis at the onset of jaundice, possibly other manifestations of decompensated liver disease such as ascites and encephalopathy, in the context of excessive alcohol ingestion. However in an excellent study by Hislop et al, patients throughout Scotland and North East England were biopsied in the assessment of alcoholic liver disease.2 It is clear from this that there is a discrepancy between the histological picture of alcoholic hepatitis and the commonly recognised presentation of the condition (see Table 1). Only 65% of patients with histological evidence of alcoholic hepatitis in this study were jaundiced and only 5% had signs of encephalopathy.

So the practical clinical question is how definite can we be about a diagnosis of alcoholic hepatitis 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 many studies which rely upon the modified discriminant function (mDF; see below) as a diagnostic criterion.2–9 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% (see Table 2).10–14 Therefore it seems possible to determine criteria for the diagnosis of clinically relevant alcoholic hepatitis without reliance upon histology. These are: a history of recent excessive alcohol ingestion; serum bilirubin >80 µmol/l; AST <500 iu (or ALT <300 iu); and exclusion of autoimmune, chronic viral or malignant liver disease. Characteristic features of alcoholic hepatitis (but not necessary for diagnosis) include pyrexia, hepatomegaly, a hepatic bruit, ascites, encephalopathy, an AST:ALT ratio greater than 1.5, and a peripheral leucocytosis.

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

**ASSESSMENT OF SEVERITY (TABLES 3 AND 4)**

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 those patients with a poor prognosis, but also to target treatment effectively. In 1978 the DF was first described in a placebo-controlled study of the benefit of corticosteroid therapy in 55 patients with alcoholic hepatitis.15 The DF was calculated between 7 and 12 days after admission. Patients with a DF greater than 9 and treated with placebo had a 25% 28-day survival while those with a score less than or equal to 93 had a survival...
of 100%. In 1989 the DF was modified in the context of a further placebo controlled corticosteroid trial involving 66 patients. A modified Discriminant Function of greater than 32 and/or the presence of encephalopathy in placebo treated patients was associated with a 65% 28-day survival. A recent 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 mDF greater than or equal to 32, while those with a score less than 32 had a survival of 93%.

In our clinical experience the mDF does not clearly identify those patients at greatest risk of death. We have recently described the GAHS for the assessment of patients presenting with a clinical diagnosis of alcoholic hepatitis. This score was derived from a population of 241 patients from Glasgow. Five variables were identified of predictive value for 28 and 84 day outcome. These were age, serum bilirubin, prothrombin time ratio (or INR), peripheral white cell count, and blood urea. This score was validated in a separate cohort of 195 patients from throughout the UK. None of these patients received corticosteroid, pentoxifylline or anti-TNF treatment. The GAHS proved to be more specific for mortality and had a greater overall accuracy than the mDF (see Table 5). It was superior to the mDF on area under the receiver operator curve (AUROC) analysis (0.783 compared with 0.721; p=0.014).

Recently, the MELD has been advocated in the assessment of alcoholic hepatitis. Three studies have compared the MELD with the mDF. None of these was able to demonstrate superiority of the MELD compared with the mDF on AUROC analysis. Another difficulty with the MELD assessment of alcoholic hepatitis is in finding the optimal cut point. One study identified a cut-point of 18 for an admission MELD score and a cut-point of 20 for the score calculated after one week. Another study identified two cut points: 22 for 30 day mortality and 21 for 90 day mortality for admission MELD scores. A third study identified the optimal cut point to be 11. In contrast, the GAHS has a constant cut-point of nine for scores calculated on admission or on day seven for both 28 and 84 day mortality. In addition, the GAHS appears to be accurate, irrespective of whether the INR or the prothrombin time ratio is used, and does not rely upon creatinine measurement. The measurement of serum creatinine is based on the Jaffe reaction by many analysers. Unless a correction is performed, the creatinine value will be underestimated in the context of hyperbilirubinaemia. Such biochemical correction may not be immediately available, thus rendering a creatinine based score inapplicable in many clinical situations.

**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 is required. In addition, patients with alcoholic hepatitis often have significant protein-energy malnutrition. Nutritional support is vital for these patients. Several randomised trials have explored the use of parenteral and enteral nutritional support in alcoholic hepatitis. The methodology of these studies has been variable and a clear improvement in survival has not been demonstrated. However there have been surrogate markers of benefit with improvements in liver blood tests, and 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 mDF greater than 32. However this study used a specific formulation of feed (‘Hepatical’) 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 potential benefit.

---

**Figure 1A**

![Effect of Corticosteroids and Pentoxifylline upon Survival relative to GAHS. A) Survival at Day 28 and Day 84 in Patients with an mDF ≥32 and a GAHS <9: Relative to the GAHS and Corticosteroid/ Pentoxifylline Treatment. B) Survival at Day 28 and Day 84 in Patients with an mDF ≥32 and a GAHS ≥9: Relative to the GAHS and Corticosteroid/ Pentoxifylline Treatment. (* = p<0.05 cf no treatment. # = p<0.005 cf no treatment.)](image)

**Figure 1B**

![Effect of Corticosteroids and Pentoxifylline upon Survival relative to GAHS. A) Survival at Day 28 and Day 84 in Patients with an mDF ≥32 and a GAHS <9: Relative to the GAHS and Corticosteroid/ Pentoxifylline Treatment. B) Survival at Day 28 and Day 84 in Patients with an mDF ≥32 and a GAHS ≥9: Relative to the GAHS and Corticosteroid/ Pentoxifylline Treatment. (* = p<0.05 cf no treatment. # = p<0.005 cf no treatment.)](image)
### SPECIFIC TREATMENT

#### Corticosteroids

Since 1971, there have been 13 randomised studies and four meta-analyses investigating the role of corticosteroid therapy for this condition.1 Despite this apparent wealth of evidence, controversy persists. The inclusion criteria for these trials varied widely and the results have been equally variable. None of these studies reached an adequate statistical power to make a statement with 80% confidence. Most recently, there has been a re-analysis of three recent randomised controlled trials only including patients with a mDF greater than 32 which seem to indicate a significant benefit from corticosteroid therapy.17 Patients treated with corticosteroids had a 28-day survival of 84-6% compared with 65-1% for placebo treated patients (p=0-001). Advocates of corticosteroids cite significant improvement in the short to medium term mortality, whilst detractors cite the risks of sepsis and gastrointestinal haemorrhage. However, recently the American College of Gastroenterology recommended corticosteroid use for the treatment of acute alcoholic hepatitis in severe disease as indicated by a mDF of greater than 32.26 Whilst validating the GAHS, information on the response of patients to corticosteroids and pentoxifylline was also gathered. This retrospective analysis appears to indicate that even with a mDF greater than or equal to 32, patients with a GAHS less than nine do not benefit from such treatment. Patients with a GAHS greater than or equal to nine treated with either corticosteroids or pentoxifylline appear to have a sustained improvement in survival28 (see Figure 1).

It has been observed that corticosteroids can induce a rapid fall in serum bilirubin compared to the placebo treated patients.17 Patients that demonstrated and sustained this fall in bilirubin appeared to have an increased survival benefit. This work was followed up more recently with a large observational study.27 This study suggested that any fall in serum bilirubin after one week of corticosteroid treatment is indicative of treatment response and good prognosis. Patients who demonstrated a fall in bilirubin had a six month survival of 82-8% compared with 23% for those without a fall in bilirubin (p=0-00001). However, with most analytes having a co-efficient of variation of the order of 5–6%, it is perhaps surprising that such minor changes in serum bilirubin could be clinically significant. In a smaller retrospective study, we observed dramatic responses to corticosteroids amongst some, but not all, patients with severe acute alcoholic hepatitis.28 In this study group, demonstration of a 25% reduction in serum bilirubin at approximately one week was associated with a substantial and sustained reduction in mortality.

#### Pentoxifylline

Pentoxifylline has also recently been studied in the treatment of alcoholic hepatitis in one randomised controlled trial.29 Pentoxifylline is believed to act by inhibiting tumour necrosis factor alpha. This study used the rather indistinct end-point of survival ‘during the index hospitalisation’. The overall mortality 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 significantly fewer 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. The role for pentoxifylline whilst promising is as yet unproven. No study has compared the effect of pentoxifylline relative to corticosteroid therapy.

### ALCOHOLIC HEPATITIS AND SEPSIS

However many patients do not receive specific treatment for alcoholic hepatitis. All the randomised controlled studies of corticosteroids and the single study of pentoxifylline have excluded patients with evidence of sepsis. Clinicians are reluctant to prescribe specific treatment for alcoholic hepatitis in this context. However such concerns may not be warranted. Meta-analyses of the use of corticosteroids in patients with sepsis or septic shock in the intensive care environment indicated either a detrimental effect or at the least no beneficial effect of corticosteroids.30, 31 However the studies on which these analyses were based, used extremely high doses of corticosteroids often over a short period of time (for example 40 mg dexamethasone in one day). Increasingly intensive care units are using corticosteroids routinely, including in the context of sepsis. A recent study looked at the use of hydrocortisone 100 mg tds intravenously for more than five days in patients with septic shock albeit without co-existing alcoholic hepatitis.32 The survival rate and rate of shock reversal was much greater in those who received this treatment compared with placebo.

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.33, 34 There were improvements in scores of multi-organ dysfunction and advantageous changes in haemodynamic parameters.

It is possible therefore that the perceived contraindications to corticosteroids and pentoxifylline in alcoholic hepatitis may not be as great as generally accepted. This can only be clarified by performing randomised studies in this difficult group of patients with both sepsis and alcoholic hepatitis.
REFERENCES

1 Health Economics Unit, Scottish Executive. Cost to society of alcohol misuse in Scotland, an update to alcohol misuse in Scotland trends and costs (Scottish Executive, October 2001). 2004; www.scotland.gov.uk


CONCLUSIONS (SEE FIGURE 2)

The study and management of alcoholic hepatitis has been fraught by disagreement regarding its diagnosis, assessment and treatment. For progress to be made, consensus is required upon a clinical definition of alcoholic hepatitis, not based upon pathological criteria, and upon a universally applicable score of severity. Patients with alcoholic hepatitis require nutritional support and surveillance for sepsis. Patients with severe disease (mDF greater than or equal to 32, or more specifically GAHS greater than or equal to nine) may benefit from corticosteroids, and perhaps pentoxifylline. Patients with concomitant sepsis, or who are unresponsive to corticosteroids, remain problematic and have a high mortality. It is this groups of patients for whom further studies are necessary. However for those patients with sepsis, broadening the indications for corticosteroids and pentoxifylline may be beneficial.
Early change in bilirubin levels is an important prognostic factor in severe alcoholic hepatitis treated with prednisolone. Hepatol 2003; 38:1363–9


BOOKS YOU SHOULD READ

The Medical Detective by Sandra Hempel. Granta Publications; 2006 £18.99

The Ghost Map by Steven Johnson. Allen Lane; 2006 £16.99

The central figures in these two books are Dr John Snow and the Rev Henry Whitehead. In a short life of 45 years, John Snow came from humble origins to become one of the best-known doctors in London. More important, his scientific rigour, indefatigable energy and refusal to be discouraged by the opposition (even ridicule) of the medical establishment, allowed him to identify cholera as a water-borne disease, consign the accepted 'miasma' theories of its spread to history, allow effective cholera prevention; and found the discipline of epidemiology. He did all this in his 'spare time', and earned his living by making ether and chloroform anaesthesia predictable and safe. He also gave chloroform to Queen Victoria in childbirth, so making it socially acceptable for that purpose.

Henry Whitehead could hardly have been more different. A product of Oxford University, he was a priest at St Luke’s church in Soho during the cholera outbreak around Broad Street in 1854. His commitment to and compassion for the people of Soho gave him an intimate ‘on the ground’ knowledge of the pattern of cholera spread in the community which contributed substantially to Snow’s evidence on how this had occurred. These men were medical giants, and they deserve to be better known.

However, these two well-written books are more than histories of Snow and Whitehead. Furthermore, they are very different but can be read together with pleasure. Hempel gives a fascinating account of the spread of cholera across Europe and its eventual spread into England in the early nineteenth century. Johnson considers the place of urbanisation in human progress and the role of the city in favouring massive disease outbreaks (especially cholera). He points to Snow’s and Whitehead’s painstaking scientific fact-finding as the way in which increasingly urbanised humans should face future challenges to cities. Both deal starkly with the suffering of the poor.

Two aspects of particular interest to doctors stand out from both books. First, cholera caused hundreds of thousands of deaths which doctors were helpless to prevent. Countless astonishing ‘impression-based’ treatments failed and caused terrible suffering. Second, the medical leaders of the day, separated from the medical frontline and certain of their miasmatic theories, were unable to appreciate Snow’s work. Humility, hopefully, will lead us to learn the ‘evidence-based’ lessons Snow and Whitehead have provided and prevent us from scoffing at our predecessors.

Niall Finlayson,
Director of Communications, RCPE